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(54) Title: BIOMARKERS FOR PRE-SELECTION OF PATIENTS FOR ANTI-IGF1R THERAPY

(57) Abstract: The present invention provides methods for identifying patients whose cancers are likely to be responsive to IGF1R inhibitory anti-cancer therapy along with methods for treating such patients. Patients identified by a method of the present invention can be treated with any of several known IGF1R inhibitory agents including antibodies, small molecule inhibitors and anti-sense nucleic acids.



WO 2006/060419 A2

BIOMARKERS FOR PRE-SELECTION OF PATIENTS FOR ANTI-IGF1R THERAPY

The present application claims the benefit of U.S. provisional patent application no. 60/633,156; filed December 3, 2004, which is herein incorporated by reference in its entirety.

Field of the Invention

The present invention relates to methods for selecting patients for anti-cancer therapy.

Background of the Invention

The insulin-like growth factors, also known as somatomedins, include insulin-like growth factor-I (IGF-I) and insulin-like growth factor-II (IGF-II) (Klapper, *et al.*, (1983) *Endocrinol.* 112:2215 and Rinderknecht, *et al.*, (1978) *Febs.Lett.* 89:283). These growth factors exert mitogenic activity on various cell types, including tumor cells (Macaulay, (1992) *Br. J. Cancer* 65:311), by binding to a common receptor named the insulin-like growth factor receptor-1 (IGF1R) (Sepp-Lorenzino, (1998) *Breast Cancer Research and Treatment* 47:235). Interaction of IGFs with IGF1R activates the receptor by triggering autophosphorylation of the receptor on tyrosine residues (Butler, *et al.*, (1998) *Comparative Biochemistry and Physiology* 121:19). Once activated, IGF1R, in turn, phosphorylates intracellular targets to activate cellular signaling pathways. This receptor activation is critical for stimulation of tumor cell growth and survival. Therefore, inhibition of IGF1R activity represents a valuable potential method to treat or prevent growth of human cancers and other proliferative diseases.

Several lines of evidence indicate that IGF-I, IGF-II and their receptor IGF1R are important mediators of the malignant phenotype. Plasma levels of IGF-I have been found to be the strongest predictor of prostate cancer risk (Chan, *et al.*, (1998) *Science* 279:563) and similar epidemiological studies strongly link plasma IGF-I levels with breast, colon and lung cancer risk.

Overexpression of Insulin-like Growth Factor Receptor-I has also been demonstrated in several cancer cell lines and tumor tissues. IGF1R is overexpressed in 40% of all breast cancer cell lines (Pandini, *et al.*, (1999) *Cancer Res.* 5:1935) and in 15% of lung cancer cell lines. In breast cancer tumor tissue, IGF1R is overexpressed 6-14 fold and IGF1R exhibits 2-4 fold higher kinase activity as compared to normal tissue (Webster, *et al.*, (1996) *Cancer Res.* 56:2781 and Pekonen, *et al.*, (1998) *Cancer Res.* 48:1343).

Ninety percent of colorectal cancer tissue biopsies exhibit elevated IGF1R levels wherein the extent of IGF1R expression is correlated with the severity of the disease. Analysis of primary cervical cancer cell cultures and cervical cancer cell lines revealed 3- and 5-fold overexpression of IGF1R, respectively, as compared to normal ectocervical cells (Steller, *et al.*, (1996) Cancer Res. 56:1762). Expression of IGF1R in synovial sarcoma cells also correlated with an aggressive phenotype (*i.e.*, metastasis and high rate of proliferation; Xie, *et al.*, (1999) Cancer Res. 59:3588).

Currently, there are several known anti-cancer therapies that target IGF1R. For example, anti-IGF1R antibodies are owned by Schering Corp (see WO 2003/100008); Pfizer (see WO 2002/53596 or WO 2004/71529); Pierre Fabre medicament (see WO 2003/59951), Pharmacia Corp. (see WO 2004/83248), Immunogen, Inc. (see WO 2003/106621), Hoffman La Roche (see WO 2004/87756) and Imclone Systems Inc. (IMC-A12; see Burtrum *et. al* Cancer Research 63:8912-8921(2003)). Additionally, Novartis owns a small molecule IGFR inhibitor, NVP-ADW-742 (see WO 2002/92599) as does Biotech Research Ventures PTE Ltd (see WO 2003/39538). Antisense Therapeutics Ltd. also owns an anti-sense therapy that inhibits IGF1R expression, ATL-1101.

Agents that decrease IGF1R function and/or expression are effective in the treatment of some cancer patients. However, it is expected that a portion of cancer patients may not respond to such treatments. Therefore, a need exists in the art for a method to identify specific cancer populations and/or specific cancer patients who are most likely to respond to one or more anti-cancer therapies that target IGF1R.

Summary of the Invention

The present invention provides, *inter alia*, a method for treating cancers by pre-selecting patients whose tumors express appreciable levels of IGF-II and/or phosphorylated IRS-1 (insulin receptor substrate-1), thereby increasing the likelihood of a response, in the patient, to therapeutics targeting IGF1R.

The present invention provides a method for treating a tumor in a patient comprising (a) selecting a patient or patient population having a tumor known to express one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;

- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R; and

(b) administering to said patient a therapeutically effective amount of an IGF1R inhibitory agent.

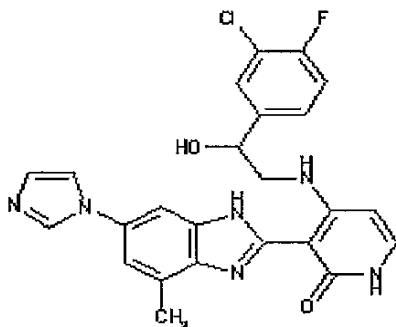
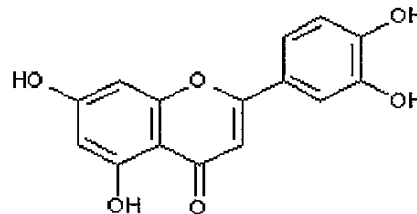
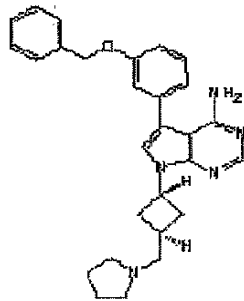
The present invention comprises a method for treating a tumor in a patient comprising: (a) selecting a patient having a tumor expressing one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R; and

(b) administering to said patient a therapeutically effective amount of an IGF1R inhibitory agent. In an embodiment of the invention, the cancer is selected from the group consisting of bladder cancer, Wilm's cancer, bone cancer, prostate cancer, lung cancer, non-small cell lung cancer (NSCLC), colon cancer, rectal cancer, colorectal cancer, endometrial cancer, multiple myeloma, estrogen receptor-positive breast cancer, estrogen receptor-negative breast cancer, cervical cancer, synovial sarcoma, ovarian cancer, pancreatic cancer, neuroblastoma, rhabdomyosarcoma, osteosarcoma and vasoactive intestinal peptide secreting tumors. In an embodiment of the invention, the agent is selected from the group consisting of an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R and is a member selected from the group consisting of: (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; (ii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98; (iii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; and (iv) an isolated single-chain

antibody (scfv) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-51; or

(v)



or ATL-1101. In an embodiment of the invention, the

isolated antibody or antigen-binding fragment thereof comprises: (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98; (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72; (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793; (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; and/or (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216. In an embodiment of the invention, phosphorylation of tyrosine on IRS-1 or IGF1R is determined by western blot analysis,

ELISA or flow cytometry analysis. In an embodiment of the invention, IGF-II expression is determined by western blot analysis, ELISA, quantitative PCR or by northern blot analysis. In an embodiment of the invention, IGF1R expression is determined by western blot analysis or ELISA.

5 The present invention provides a method for selecting a therapy for a patient or a patient population with a tumor, comprising: (a) determining whether the patient's tumor is known to express one or more of the following:

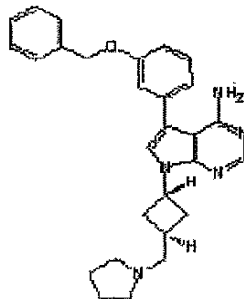
- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- 10 (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R; and/or

(b) determining whether the patient's tumor expresses one or more of the following:

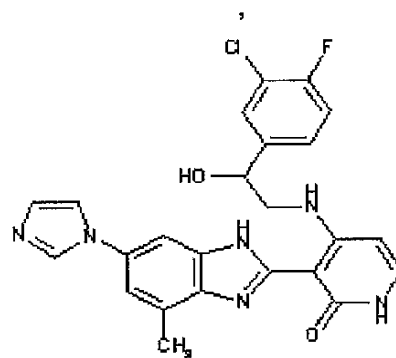
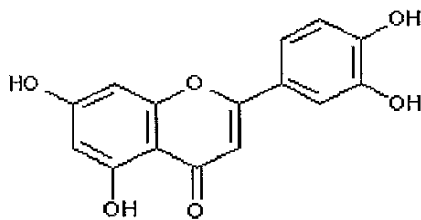
- 15 (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- 20 (vi) IGF1R; and

(c) selecting an IGF1R inhibitory agent as the therapy if the patient's tumor is known to express one or more of (i)-(vi) and/or if the patient's tumor expresses one or more of (i)-(vi). In an embodiment of the invention, the agent is selected from the group consisting of an isolated antibody or antigen-binding fragment thereof that binds specifically to human
25 IGF1R and is a member selected from the group consisting of: (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; (ii) an isolated antibody or antigen-binding
30 fragment thereof comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98; (iii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; and (iv) an isolated single-chain

antibody (scfv) comprising an amino acid sequence selected from the group consisting of



SEQ ID NOs: 46-51; or (v)



or ATL-1101.

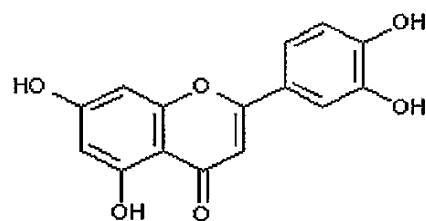
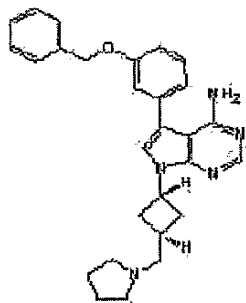
In an embodiment of the invention, the isolated antibody or antigen-binding fragment

thereof comprises: (i) an isolated immunoglobulin heavy chain comprising an amino acid
 5 sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98; (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72; (iii) an isolated antibody produced by a hybridoma deposited at the
 10 American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793; (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; and/or (v) an isolated antibody
 15 comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

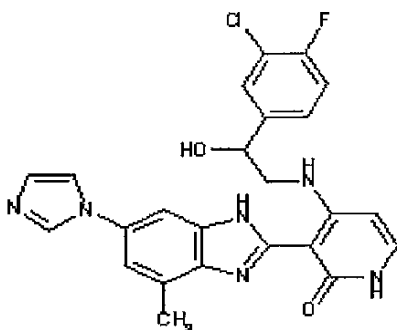
20 The present invention also provides a method for advertising an IGF1R inhibitory agent or a pharmaceutically acceptable composition thereof comprising promoting, to a

target audience, the use of the agent or pharmaceutical composition thereof for treating a patient or patient population whose tumors express or are known to express one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
 - 5 (ii) IRS-1 phosphorylation on tyrosine 612;
 - (iii) IRS-1 phosphorylation on any tyrosine;
 - (iv) IGF-II;
 - (v) IGF1R phosphorylation on any tyrosine; or
 - (vi) IGF1R.
- 10 In an embodiment of the invention, the agent is selected from the group consisting of an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R and is a member selected from the group consisting of: (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ
- 15 ID NO: 8 and/or one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; (ii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98; (iii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from
- 20 a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; and (iv) an isolated single-chain antibody (scfv) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:



46-51; or (v)



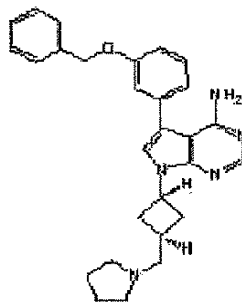
or ATL-1101. In an embodiment of the invention, the

isolated antibody or antigen-binding fragment thereof comprises: (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98; (ii) an isolated
 5 immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72; (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793; (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically
 10 to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; and/or (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded
 15 by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

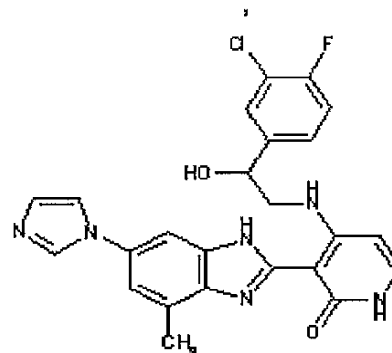
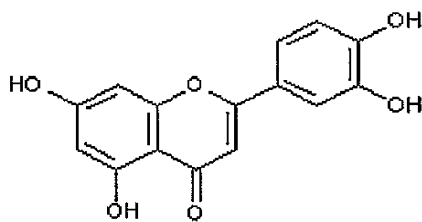
The present invention also provides an article of manufacture comprising, packaged together, a pharmaceutical composition comprising an IGF1R inhibitory agent and a pharmaceutically acceptable carrier and a label stating that the agent or
 20 pharmaceutical composition is indicated for treating patients having a tumor expressing or known to express one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- 25 (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R.

In an embodiment of the invention, the agent is selected from the group consisting of an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R and is a member selected from the group consisting of: (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; (ii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98; (iii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; and (iv) an isolated single-chain antibody (scfv) comprising an amino acid sequence selected from the group consisting of



SEQ ID NOs: 46-51; or (v)



or ATL-1101.

In an embodiment of the invention, the isolated antibody or antigen-binding fragment thereof comprises: (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98; (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72; (iii) an isolated antibody produced by a hybridoma deposited at the

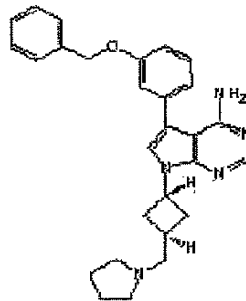
American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793; (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; and/or (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

The present invention further provides a method for manufacturing an IGF1R inhibitory agent or a pharmaceutical composition thereof comprising combining in a package the agent or pharmaceutical composition and a label stating that the agent or pharmaceutical composition is indicated for treating patients having a tumor expressing or known to express one or more of the following:

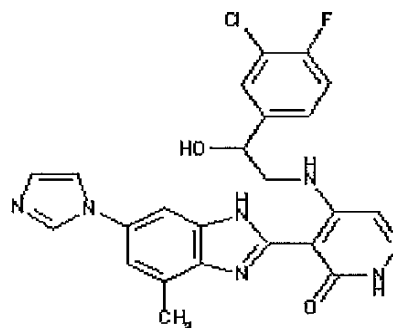
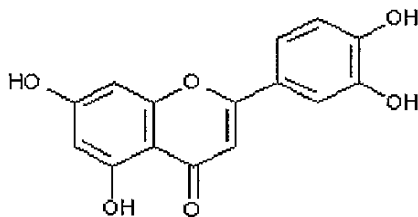
- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R.

In an embodiment of the invention, the agent is selected from the group consisting of an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R and is a member selected from the group consisting of: (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; (ii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98; (iii) an isolated antibody or antigen-binding fragment thereof comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; and (iv) an isolated single-chain antibody (scfv) comprising an amino acid sequence selected from the group consisting of

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SEQ ID NOs: 46-51; (v)



or ATL-1101.

In an embodiment of the invention, the isolated antibody or antigen-binding fragment thereof comprises: (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98; (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72; (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793; (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; and/or (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

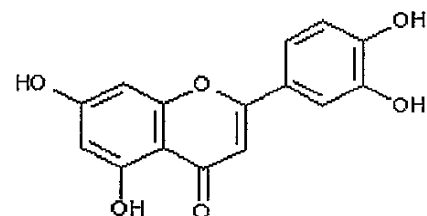
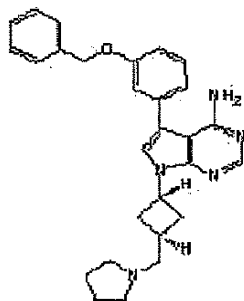
The present invention also provides a method for identifying a patient whose tumor is likely to be responsive to an IGF1R inhibitory agent comprising: (a) determining whether the patient has a tumor known to express one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- 5 (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R; and/or

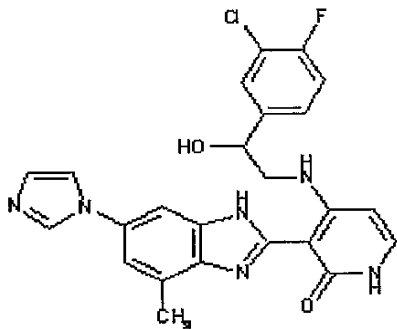
(b) determining whether the patient has a tumor expressing one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- 10 (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R.

In an embodiment of the invention, the agent is selected from the group consisting of an
 15 isolated antibody or antigen-binding fragment thereof that binds specifically to IGF1R and
 is a member selected from the group consisting of: (i) an isolated antibody or antigen-
 binding fragment thereof that binds specifically to human IGF1R comprising one or more
 CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8
 and/or a one or more CDRs from a heavy chain variable region comprising amino acids
 20 20-137 of SEQ ID NO: 10; (ii) an isolated antibody or antigen-binding fragment thereof
 comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino
 acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98; (iii) an isolated
 antibody or antigen-binding fragment thereof comprising one or more CDRs from a light
 chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-
 25 34, 39, 40, 41, 42, 44 or 58-72; and (iv) an isolated single-chain antibody (scfv)
 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:



46-51; or (v)



or ATL-1101. In an embodiment of the invention, the

isolated antibody or antigen-binding fragment thereof comprises: (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98; (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72; (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793; (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; and/or (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

Brief Description of the Figures

Figure 1. IRS-1 Phosphorylation is Higher in Human Lung Tumor vs. Normal Tissue Samples. Western blot analysis results for normal and tumor tissue samples from four different patients. Lanes marked "T" contained tumor tissue and lanes marked "N" contained normal tissue.

Figure 2. Antibody 19D12/15H12 LCF/HCA: *In Vivo* Efficacy. The level of tumor growth inhibition observed in xenograft mice administered antibody 19D12/15H12 LCF/HCA is indicated along with the type of tumor evaluated and the cell line used to establish each tumor.

Figure 3. *In Vivo* Efficacy of 19D12/15H12 LCF/HCA Correlates with Sensitivity of IRS-1 Phosphorylation to IGF-I. In the "-" and "+" lanes, the quantity of phosphorylated

IRS-1, in each cell line evaluated, is shown in the absence and presence of IGF-I, respectively. The level of *in vivo* efficacy of 19D12/15H12 LCF/HCA at inhibiting growth of the indicated cell line (see figure 2) is also indicated.

Figure 4. Overexpression of *IGF-II* mRNA in Human Ovarian Tumor Samples.

5 The normalized level of *IGF-II* mRNA expression observed in each of the 20 normal ovarian tissue samples and 36 cancerous ovarian tissue samples is shown.

Figure 5. Overexpression of *IGF-II* mRNA in Human Colorectal Tumor Samples.

The normalized level of *IGF-II* mRNA expression observed in each of the 36 normal ovarian tissue samples and 36 cancerous colorectal tissue samples is shown.

10

Detailed Description of the Invention

The present invention provides a method for treating cancer or for identifying patients whose cancer is likely to be responsive to an IGF1R inhibitory agent. The method is useful, *inter alia*, for increasing the likelihood that administration of an IGF1R
15 inhibitory anti-cancer therapy to a patient will be efficacious.

The terms "IGF1R", "IGFR1", "Insulin-like Growth Factor Receptor-I" and "Insulin-like Growth Factor Receptor, type I" are well known in the art. Although IGF1R may be from any organism, it is preferably from an animal, more preferably from a mammal (*e.g.*, mouse, rat, rabbit, sheep or dog) and most preferably from a human. The nucleotide and
20 amino acid sequence of a typical human IGF1R precursor has the Genbank Accession No. X04434 or NM_000875. Cleavage of the precursor (*e.g.*, between amino acids 710 and 711) produces an α -subunit and a β -subunit which associate to form a mature receptor.

The terms "IGF-I" "Insulin-like Growth Factor-I" and "Insulin-like Growth Factor, type I" are also well known in the art. The terms "IGF-II" "Insulin-like Growth Factor-II" and "Insulin-like Growth Factor, type II" are also well known in the art. Although IGF-I or IGF-II may be from any organism, they are preferably from an animal, more preferably from a mammal (*e.g.*, mouse, rat, rabbit, sheep or dog) and most preferably from a human. The nucleic acid and amino acid sequence of typical, human IGF-I and IGF-II
25 have the Genbank Accession No. XM_052648 and NM_000612, respectively.

30

IGF1R inhibitory agents

The term "IGF1R inhibitory agent" includes any substance that decreases the expression, ligand binding, kinase activity or any other biological activity of IGF1R that will

elicit a biological or medical response of a tissue, system, subject or patient that is being sought by the administrator (such as a researcher, doctor or veterinarian) which includes any measurable alleviation of the signs, symptoms and/or clinical indicia of cancer (e.g., tumor growth) and/or the prevention, slowing or halting of progression or metastasis of cancer to any degree.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention is any isolated anti-insulin-like growth factor receptor-1 (IGF1R) antibody or fragment thereof (e.g., monoclonal antibodies (e.g., fully human monoclonal antibodies), polyclonal antibodies, bispecific antibodies, Fab antibody fragments, F(ab)₂ antibody fragments, Fv antibody fragments (e.g., VH or VL), single chain Fv antibody fragments, dsFv antibody fragments, humanized antibodies, chimeric antibodies or anti-idiotypic antibodies) such as any of those disclosed in any of Burtrum *et. al*/ Cancer Research 63:8912-8921(2003); in French Patent Applications FR2834990, FR2834991 and FR2834900 and in PCT Application Publication Nos. WO 03/100008; WO 03/59951; WO 04/71529; WO 03/106621; WO 04/83248; WO 04/87756 and WO 02/53596.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention is an isolated anti-insulin-like growth factor receptor-1 (IGF1R) antibody comprising a mature or unprocessed 19D12/15H12 Light Chain-C, D, E or F and a mature 19D12/15H12 heavy chain-A or B.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention is an isolated antibody that specifically binds to IGF1R that comprises one or more complementarity determining regions (CDRs) of 19D12/15H12 Light Chain-F and/or 19D12/15H12 heavy chain-A (e.g., all 3 light chain CDRs and all 3 heavy chain CDRs).

The amino acid and nucleotide sequences of the 19D12/15H12 antibody chains are shown below. Dotted, underscored type indicates the signal peptide. Solid underscored type indicates the CDRs. Plain type indicates the framework regions. Mature fragments lack the signal peptide.

Modified 19D12/15H12 Light Chain-C (SEQ ID NO: 1)

ATG TCG CCA TCA CAA CTC ATT GGG TTT CTG CTG CTC TGG GTT CCA GCC TCC

AGG GGT GAA ATT GTG CTG ACT CAG AGC CCA GAC TCT CTG TCT GTG ACT CCA

16

GGC GAG AGA GTC ACC ATC ACC TGC CGG GCC AGT CAG AGC ATT GGT AGT AGC
TTA CAC TGG TAC CAG CAG AAA CCA GGT CAG TCT CCA AAG CTT CTC ATC AAG
 5 TAT GCA TCC CAG TCC CTC TCA GGG GTC CCC TCG AGG TTC AGT GGC AGT GGA
 TCT GGG ACA GAT TTC ACC CTC ACC ATC AGT AGC CTC GAG GCT GAA GAT GCT
 10 GCA GCG TAT TAC TGT CAT CAG AGT AGT CGT TTA CCT CAC ACT TTC GGC CAA
 GGG ACC AAG GTG GAG ATC AAA CGT ACG

(SEQ ID NO: 2)

15 M S P S Q L I G F L L L W V P A S
 R G E I V L T Q S P D S L S V T P
 20 G E R V T I T C R A S Q S I G S S
 L H W Y Q Q K P G Q S P K L L I K
 Y A S Q S L S G V P S R F S G S G
 25 S G T D F T L T I S S L E A E D A
 A A Y Y C H Q S S R L P H T F G Q
 G T K V E I K R T

Modified 19D12/15H12 Light Chain-D (SEQ ID NO: 3)

ATG TCG CCA TCA CAA CTC ATT GGG TTT CTG CTG CTC TGG GTT CCA GCC TCC
 35 AGG GGT GAA ATT GTG CTG ACT CAG AGC CCA GAC TCT CTG TCT GTG ACT CCA
 GGC GAG AGA GTC ACC ATC ACC TGC CGG GCC AGT CAG AGC ATT GGT AGT AGC
 40 TTA CAC TGG TAC CAG CAG AAA CCA GGT CAG TCT CCA AAG CTT CTC ATC AAG
TAT GCA TCC CAG TCC CTC TCA GGG GTC CCC TCG AGG TTC AGT GGC AGT GGA
 TCT GGG ACA GAT TTC ACC CTC ACC ATC AGT AGC CTC GAG GCT GAA GAT TTC
 45 GCA GTG TAT TAC TGT CAT CAG AGT AGT CGT TTA CCT CAC ACT TTC GGC CAA
 GGG ACC AAG GTG GAG ATC AAA CGT ACG

(SEQ ID NO: 4)

50 M S P S Q L I G F L L L W V P A S
 R G E I V L T Q S P D S L S V T P

17

G E R V T I T C R A S Q S I G S S
L H W Y Q Q K P G Q S P K L L I K
 5 Y A S Q S L S G V P S R F S G S G
 S G T D F T L T I S S L E A E D F
 10 A V Y Y C H Q S S R L P H T F G Q
 G T K V E I K R T

Modified 19D12/15H12 Light Chain-E (SEQ ID NO: 5)

15 ATG TCG CCA TCA CAA CTC ATT GGG TTT CTG CTG CTC TGG GTT CCA GCC TCC
AGG GGT GAA ATT GTG CTG ACT CAG AGC CCA GGT ACC CTG TCT GTG TCT CCA
 GGC GAG AGA GCC ACC CTC TCC TGC CGG GCC AGT CAG AGC ATT GGT AGT AGC
 20 TTA CAC TGG TAC CAG CAG AAA CCA GGT CAG GCT CCA AGG CTT CTC ATC AAG
TAT GCA TCC CAG TCC CTC TCA GGG ATC CCC GAT AGG TTC AGT GGC AGT GGA
 25 TCT GGG ACA GAT TTC ACC CTC ACC ATC AGT AGA CTG GAG CCT GAA GAT GCT
 GCA GCG TAT TAC TGT CAT CAG AGT AGT CGT TTA CCT CAC ACT TTC GGC CAA
 GGG ACC AAG GTG GAG ATC AAA CGT ACA

30

(SEQ ID NO: 6)

M S P S Q L I G F L L L W V P A S
 35 R G E I V L T Q S P G T L S V S P
 G E R A T L S C R A S Q S I G S S
 40 L H W Y Q Q K P G Q A P R L L I K
Y A S Q S L S G I P D R F S G S G
 S G T D F T L T I S R L E P E D A
 45 A A Y Y C H Q S S R L P H T F G Q
 G T K V E I K R T

19D12/15H12 Light Chain-F (LCF; SEQ ID NO: 7)

50

ATG TCG CCA TCA CAA CTC ATT GGG TTT CTG CTG CTC TGG GTT CCA GCC TCC
 55 AGG GGT GAA ATT GTG CTG ACT CAG AGC CCA GGT ACC CTG TCT GTG TCT CCA
 GGC GAG AGA GCC ACC CTC TCC TGC CGG GCC AGT CAG AGC ATT GGT AGT AGC

18

TTA CAC TGG TAC CAG CAG AAA CCA GGT CAG GCT CCA AGG CTT CTC ATC AAG
 TAT GCA TCC CAG TCC CTC TCA GGG ATC CCC GAT AGG TTC AGT GGC AGT GGA
 5 TCT GGG ACA GAT TTC ACC CTC ACC ATC AGT AGA CTG GAG CCT GAA GAT TTC
 GCA GTG TAT TAC TGT CAT CAG AGT AGT CGT TTA CCT CAC ACT TTC GGC CAA
 GGG ACC AAG GTG GAG ATC AAA CGT ACA

(SEQ ID NO: 8)

M S P S Q L I G F L L L W V P A S
 15 R G E I V L T Q S P G T L S V S P
 G E R A T L S C R A S Q S I G S S
 20 L H W Y Q Q K P G Q A P R L L I K
 Y A S Q S L S G I P D R F S G S G
 S G T D F T L T I S R L E P E D F
 25 A V Y Y C H Q S S R L P H T F G Q
 G T K V E I K R T

19D12/15H12 heavy chain-A (HCA; SEQ ID NO: 9)

30 ATG GAG TTT GGG CTG AGC TGG GTT TTC CTT GTT GCT ATA TTA AAA GGT GTC
 CAG TGT GAG GTT CAG CTG GTG CAG TCT GGG GGA GGC TTG GTA AAG CCT GGG
 35 GGG TCC CTG AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTC AGT AGC TTT
 GCT ATG CAC TGG GTT CGC CAG GCT CCA GGA AAA GGT CTG GAG TGG ATA TCA
 40 GTT ATT GAT ACT CGT GGT GCC ACA TAC TAT GCA GAC TCC GTG AAG GGC CGA
 TTC ACC ATC TCC AGA GAC AAT GCC AAG AAC TCC TTG TAT CTT CAA ATG AAC
 AGC CTG AGA GCC GAG GAC ACT GCT GTG TAT TAC TGT GCA AGA CTG GGC AAC
 45 TTC TAC TAC GGT ATG GAC GTC TGG GGC CAA GGG ACC ACG GTC ACC GTC TCC
 TCA

(SEQ ID NO: 10)

50 Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Leu Lys Gly Val
 Gln Cys Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Lys Pro Gly
 55 Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Ser
 Val Ile Asp Thr Arg Gly Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg

Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
 Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Leu Gly Asn
Phe Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
 Ser

10 **Modified 19D12/15H12 heavy chain-B (SEQ ID NO: 11)**

ATG GAG TTT GGG CTG AGC TGG GTT TTC CTT GTT GCT ATA TTA AAA GGT GTC
CAG TGT GAG GTT CAG CTG GTG CAG TCT GGG GGA GGC TTG GTA CAG CCC GGG
 15 GGG TCC CTG AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTC AGT AGC TTT
GCT ATG CAC TGG GTT CGC CAG GCT CCA GGA AAA GGT CTG GAG TGG ATA TCA
 20 GTT ATT GAT ACT CGT GGT GCC ACA TAC TAT GCA GAC TCC GTG AAG GGC CGA
 TTC ACC ATC TCC AGA GAC AAT GCC AAG AAC TCC TTG TAT CTT CAA ATG AAC
 AGC CTG AGA GCC GAG GAC ACT GCT GTG TAT TAC TGT GCA AGA CTG GGG AAC
 25 TTC TAC TAC GGT ATG GAC GTC TGG GGC CAA GGG ACC ACG GTC ACC GTC TCC
 TCA

(SEQ ID NO: 12)

30 Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Leu Lys Gly Val
Gln Cys Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly
 35 Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Ser
 40 Val Ile Asp Thr Arg Gly Ala Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg
 Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
 Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Leu Gly Asn
 45 Phe Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
 Ser

Plasmids comprising a CMV promoter operably linked to the 15H12/19D12 LCC,
 50 LCD, LCE, LCF or to the 15H12/19D12 HCA or HCB have been deposited at the
 American Type Culture Collection (ATCC); 10801 University Boulevard; Manassas,
 Virginia 20110-2209 on May 21, 2003. The deposit names and the ATCC accession
 numbers for the plasmids are set forth below:

(1) CMV promoter-15H12/19D12 HCA (γ 4)-

55 Deposit name: "15H12/19D12 HCA (γ 4)"

ATCC accession No.: PTA-5214

(2) CMV promoter-15H12/19D12 HCB (γ 4)-

Deposit name: "15H12/19D12 HCB (γ 4)"

ATCC accession No.: PTA-5215

5 (3) CMV promoter-15H12/19D12 HCA (γ 1)-

Deposit name: "15H12/19D12 HCA (γ 1)";

ATCC accession No.: PTA-5216

(4) CMV promoter-15H12/19D12 LCC (κ)-

Deposit name: "15H12/19D12 LCC (κ)";

10 ATCC accession No.: PTA-5217

(5) CMV promoter-15H12/19D12 LCD (κ)-

Deposit name: "15H12/19D12 LCD (κ)";

ATCC accession No.: PTA-5218

(6) CMV promoter-15H12/19D12 LCE (κ)-

15 Deposit name: "15H12/19D12 LCE (κ)";

ATCC accession No.: PTA-5219

(7) CMV promoter-15H12/19D12 LCF (κ)-

Deposit name: "15H12/19D12 LCF (κ)";

ATCC accession No.: PTA-5220

20 All restrictions on access to the plasmids deposited in ATCC will be removed upon grant of a patent. In an embodiment of the present invention, an anti-IGF1R antibody or antigen-binding fragment thereof of the invention comprises any of the CDRs or Ig heavy or light chains or variable regions thereof in any of PTA-5214-PTA-5220. In an embodiment of the invention, the antibody comprises a light chain encoded by the plasmid
25 deposited under number PTA-5220 and a heavy chain encoded by the plasmid deposited under number PTA-5214 or PTA-5216.

In an embodiment, an antibody that binds "specifically" to human IGF1R binds with Kd of about 1.28×10^{-10} M or less by Biacore measurement or with a Kd of about 2.05×10^{-12} or less by KinExA measurement.

30 In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention comprises any light chain immunoglobulin and/or a heavy chain immunoglobulin as set forth in Published

International Application No. WO 2002/53596 which is herein incorporated by reference in its entirety. For example, in an embodiment, the antibody comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 6, 10, 14, 18, 22, 47 and 51 as set forth in WO 2002/53596 and/or a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 8, 12, 16, 20, 24, 45 and 49 as set forth in WO 2002/53596.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention comprises any light chain immunoglobulin and/or a heavy chain immunoglobulin as set forth in Published

International Application No. WO 2003/59951 which is herein incorporated by reference in its entirety. For example, in an embodiment, the antibody comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 61 and 65 as set forth in WO 2003/59951 and/or a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 69, 75, 79 and 83 as set forth in WO 2003/59951.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention comprises any light chain immunoglobulin and/or a heavy chain immunoglobulin as set forth in Published

International Application No. WO 2004/83248 which is herein incorporated by reference in its entirety. For example, in an embodiment, the antibody comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141 and 143 as set forth in WO 2004/83248 and/or a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140 and 142 as set forth in WO 2004/83248.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention comprises any light chain immunoglobulin and/or a heavy chain immunoglobulin as set forth in Published

International Application No. WO 2003/106621 which is herein incorporated by reference in its entirety. For example, in an embodiment, the antibody comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8-12, 58-69, 82-86, 90, 94, 96, 98, as set forth in WO 2003/106621 and/or a heavy chain variable region comprising an amino acid sequence selected from the

group consisting of SEQ ID NOs: 7, 13, 70-81, 87, 88, 92 as set forth in WO 2003/106621.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention comprises any light chain immunoglobulin and/or a heavy chain immunoglobulin as set forth in Published International Application No. WO 2004/87756 which is herein incorporated by reference in its entirety. For example, in an embodiment, the antibody comprises a light chain variable region comprising an amino acid sequence of SEQ ID NO: 2 as set forth in WO 2004/87756 and/or a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 1 as set forth in WO 2004/87756.

Furthermore, the scope of the present invention comprises any antibody or antibody fragment comprising one or more CDRs and/or framework regions of any of the light chain immunoglobulin or heavy chain immunoglobulins set forth in WO 2002/53596; WO 2003/59951; WO 2004/83248; WO 2003/106621 or WO 2004/87756 as identified by any of the methods set forth in Chothia *et al.*, J. Mol. Biol. 186:651-663 (1985); Novotny and Haber, Proc. Natl. Acad. Sci. USA 82:4592-4596 (1985) or Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)).

In an embodiment of the invention, anti-IGF1R antibody is produced by a hybridoma that is deposited at the American Type Culture Collection under deposit no. PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793.

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence selected from the group consisting of:

1 grlggawrs1 rlscaasgft fsdyymswir qapgkglewv syissgstr
51 dyadsvkgrf tiserdnakns lylqmns1ra edtavyycvr dgvettffyy
101 yygmdvwgqg ttvtvssast kgpsvfplap csrstsesta algclvkdyf
151 pepvtvswns galtsgvhtf psca
(SEQ ID NO: 13)

1 vqllesgggl vqpqgslrls ctasgftfss yammwvrqap gkglewvsai
51 sgsggttfya dsvkgrftis rdnsrttlyl qmns1raedt avyycakdlg
101 wdsyyyyyyg mdvwgqgttv tvss
(SEQ ID NO: 14)

1 gpglvkpset ls1tctvsgg sisnyywwi rqpagkglew igriytsdsp
51 nynpslksrv tmsvdtksnq fslklsvta adtavyyca v tifgvviifd
101 ywgqgtlvtv ss
(SEQ ID NO: 15)

1 evqllesggg lvqpqgslrl scaasgftfs syamswvrqa pgkglewvsai
51 isgsggityy adsvkgrfti srdnskn1ty lqmns1raed tavyyca1dl

101 gygdffffff gmdvwgqgtt vtvss
(SEQ ID NO: 16)

1 pglvvpsetl sltctvsggs issyywswir qppgkglewi gyiyygsgtn
51 ynpslksrvt isvdtsknqf slklssvtaa dtavyycart ysssfyyym
5 101 dvwgqgttvt vss
(SEQ ID NO: 17)

1 evqllesggg lvqpggslrl scaasgftfs syamswvrqa pgkglewvsg
51 itgsggstyy adsvkgrfti srdnskntly lqmslraed tavyycakdp
101 gttvmswfd pwgqgtltvt ss
10 (SEQ ID NO: 18)

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises an immunoglobulin light chain variable region comprising an amino acid sequence selected from the group consisting of:

15 1 asvgdrvtft crasqdirrd lgwyqqkpgk apkrliyaas rlqsgvpsrf
51 sgsgsgteft ltisslqped fatyyclqhn nyptrfgqgt eveiirtvaa
101 psvfifppsd eqlksqtasv vcllnnfypr eakvqw
(SEQ ID NO: 19)

1 diqmtqfpss lsasvgdrvt itcrasqgir ndlgwyqqk gkapkrliya
20 51 asrlhrvgps rfsqsgsgte ftltisslqp edfatyyclq hnsypcsfgg
101 gtkleik
(SEQ ID NO: 20)

1 sslsasvgdr vtftcrasqd irrdlgwyqq kpgkapkrli yaasrlqsgv
51 psrfsgsgsg tefltltissl qpedefatyyc lqhnnyptrf gqgteveirr
25 (SEQ ID NO: 21)

1 diqmtqspss lsasvgdrvt itcrasqgir sdlgwfqqk gkapkrliya
51 asklhrvgps rfsqsgsgte ftltisrlqp edfatyyclq hnsypltfgg
101 gtkveik
(SEQ ID NO: 22)

30 1 gdrvtitcra sqsistflnw yqqkpgkapk llihvasslq ggvpssrfsgs
51 sggtdfthti sslqpedfat yycqqsynap ltfgggkve ik
(SEQ ID NO: 23)

1 ratlsctasq svrgrylawy qqkpgqaprl liygassrat gipdrfsgsg
51 sgtdftltis rlepedfavf ycqqygsspr tfgggtkvei k
35 (SEQ ID NO: 24)

In an embodiment of the invention, the anti-IGF1R antibody comprises a light chain immunoglobulin, or a mature fragment thereof (*i.e.*, lacking signal sequence), or variable region thereof, comprising the amino acid sequence of:

40 1 mdmrvpaql1 gl1111wfpqa rcdiqmtqsp ss1sasvgdr vtitcrasqg
51 irrdlgwyqq kpgkapkrli yaasslqsgv psrfsgsgsg tefltltissl
101 qpedefatyyc lqhnsypwtf gqgtkveikr tvaapsvfif ppsdeqlksg
151 tasvvc11nn fypreakvqw kvdnalqsgn sgesvteqds kdstyslsst
201 ltlskadyek hkvyacevth qglsspvtkf fnrgec ;
(SEQ ID NO: 25)

45 1 mdmrvpaql1 gl1111wfpqa rcdiqmtqsp ss1sasvgdr vtftcrasqd
51 irrdlgwyqq kpgkapkrli yaasrlqsgv psrfsgsgsg tefltltissl

101 gpedfatyyyc lghnnyprtf gggteveiir tvaapsvfif ppsdeqlksg
 151 tasvvcllnn fypreakvqw kvdnalqsgn sgesvteqds kdstyslsst
 201 ltlskadyek hkvyacevth qglsspvtks fnrgec ;

(SEQ ID NO: 26)

5

1 mdmrvpaql1 gl1llwfpga rcdiqmtqsp ss1sasvgdr vtitcrasgg
 51 irndlgwyqq kpgkapkrli yaasslqsgv psrfsgsgsg teftltissl
 101 gpedfatyyyc lghnsypytf gggtkleikr tvaapsvfif ppsdeqlksg
 151 tasvvcllnn fypreakvqw kvdnalqsgn sgesvteqds kdstyslsst
 201 ltlskadyek hkvyacevth qglsspvtks fnrgec ;

10

(SEQ ID NO: 27)

or

1 mdmrvpaql1 gl1llwfpga rcdiqmtgfp ss1sasvgdr vtitcrasgg
 15 51 irndlgwyqq kpgkapkrli yaasrlhrgv psrfsgsgsg teftltissl
 101 gpedfatyyyc lghnsypcsf gggtkleikr tvaapsvfif ppsdeqlksg
 151 tasvvcllnn fypreakvqw kvdnalqsgn sgesvteqds kdstyslsst
 201 ltlskadyek hkvyacevth qglsspvtks fnrgec

(SEQ ID NO: 28). In an embodiment of the invention, the signal sequence is amino acids

20

1-22 of SEQ ID NOs: 25-28. In an embodiment of the invention, the mature variable region is underscored.

In an embodiment of the invention, the anti-IGF1R antibody comprises a heavy chain immunoglobulin or a mature fragment thereof (*i.e.*, lacking signal sequence), or a variable region thereof, comprising the amino acid sequence of:

25 1 mefglswvfl vaiikgvqcq vqlvesgggl vkpggslrls caasgftfsd
 51 ymswirgap gkglewsvyi sssgstiyya dsvkgrftis rdnaknslyl
 101 qmns1raedt avyyicarvlr flewllyyyy ygmdivwggg ttvtvsaast
 151 kgpsvfplap csrstsesta algclvkdyf pepvtvswns galtsgvhtf
 201 pavlqssgly slssvvtvps snfgtqtytc nvdhkpntk vdktkverkcc
 30 251 vecppcpapp vagpsvflfp pkpkdtlmis rtpevtcvvv dvshedpevq
 301 fnwyvdgvev hnaktkpree qfnstfrvvs vltvvhqdlw ngkeykckvs
 351 nkg1papiekt tisktkgqpr epqvytlpps reemtknqvs ltclvkgfyp
 401 sdiavewesn gqpennyktt ppmldsdgsf flyskltvdk srwqqgnvfs
 451 csmhealhn hytqkslsls pgk ;

35

(SEQ ID NO: 29)

1 mefglswvfl vaiikgvqcq aqlvesgggl vkpggslrls caasgftfsd
 51 ymswirgap gkglewsvyi sssgstirdya dsvkgrftis rdnaknslyl
 40 101 qmns1raedt avyycvrdgv ettffyyyyy mdvwggggttv tvssastkgp
 151 svfplapcsr stsestaalg clvkdyfpep vtvswnsgal tsgvhtfpav
 201 lqssglysls svvtvpssnf gtqtytcnvd hkpsntkvdk tverkccvec
 251 ppcpappvag psvflfppkp kdtlmisrtp evtcvvvdvs hedpevqfnw
 301 yvdgvevhna ktkpreeqfn stfrvsvlt vvhqdwlngk eykckvsnkg
 351 lpapiektis ktkgqprepq vytlppsree mtknqvsltc lvkgfypsdi
 45 401 avewesngqp ennykttppm ldsdgsffly skltvdksrw qqgnvfscsv
 451 mhealhnhyt qksls1spgk ;

(SEQ ID NO: 30)

1 mefglswlfl vaiikgvqce vqllesgggl vqpggslrls caasgftfss
 50 51 yamswvrqap gkglewvsai sgsggstyya dsvkgrftis rdnskntlyl
 101 qmns1raedt avyycakgys sgwyyyyyyg mdvwggggttv tvssastkgp

25

151 svfplapcsr stsestaalg clvkdyfpep vtvswngal tsgvhtfpav
 201 lqssglysls svvtvpssnf gtqtytcnvd hkpsntkvdK tverkccvec
 251 ppcpappvag psvflfppkp kdtlmisrtp evtcvvvdvs hedpevqfnw
 301 yvdgvevhna ktkpreeqfn stfrvsvlt vvhqdwlngk eykckvsnkg
 5 351 lpapiektis ktkgqprepq vytlppsree mtknqvsltc lvkgfypsdi
 401 avewesngqp ennykttppm ldsdgsffly skltvdksrw qqgnvfscsv
 451 mhealhnhyt qkslslsppgk ;

(SEQ ID NO: 31)

or

1 mefglswlfl vailkgvqce vqllesgggl vqpggslrls ctasgftfss
 51 yamnwvrqap gkglewvsai sgsggttfya dsvkgrftis rdnsrttlyl
 101 qmnsdraedt avyycakdlg wsdsyyyyyg mdvwgggttv tvssastkqp
 151 svfplapcsr stsestaalg clvkdyfpep vtvswngal tsgvhtfpav
 15 201 lqssglysls svvtvpssnf gtqtytcnvd hkpsntkvdK tverkccvec
 251 ppcpappvag psvflfppkp kdtlmisrtp evtcvvvdvs hedpevqfnw
 301 yvdgvevhna ktkpreeqfn stfrvsvlt vvhqdwlngk eykckvsnkg
 351 lpapiektis ktkgqprepq vytlppsree mtknqvsltc lvkgfypsdi
 401 avewesngqp ennykttppm ldsdgsffly skltvdksrw qqgnvfscsv
 20 451 mhealhnhyt qkslslsppgk

(SEQ ID NO: 32). In an embodiment of the invention, the signal sequence is amino acids 1-19 of SEQ ID NOs: 29-32. In an embodiment of the invention, the mature variable region is underscored.

In an embodiment of the invention, the anti-IGF1R antibody comprises a light chain variable region comprising the amino acid sequence of any of SEQ ID NOs: 19-24 paired with a heavy chain variable region comprising an amino acid sequence of any of SEQ ID NOs: 13-18, respectively. In an embodiment of the invention, the anti-IGF1R antibody comprises a mature light chain variable region comprising an amino acid sequence of any of SEQ ID NOs: 25 or 26 paired with a heavy chain variable region comprising an amino acid sequence of any of SEQ ID NOs: 29 or 30. In an embodiment of the invention, the anti-IGF1R antibody comprises a mature light chain variable region comprising an amino acid sequence of any of SEQ ID NOs: 27 or 28 paired with a heavy chain variable region comprising an amino acid sequence of any of SEQ ID NOs: 31 or 32.

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises an immunoglobulin heavy chain or mature fragment or variable region of 2.12.1 fx (SEQ ID NO: 33) (in an embodiment of the invention, the leader sequence is underscored):

1 mefglswvfl vaiikgvqcc vqlvesgggl vkpggslrls caasgftfsd
 51 yymswirqap gkglewvsyi sssgstrdya dsvkgrftis rdnaknslyl
 101 qmnsdraedt avyycardgv ettfyyyyyg mdvwgggttv tvssastkqp
 151 svfplapcsr stsestaalg clvkdyfpep vtvswngal tsgvhtfpav
 201 lqssglysls svvtvpssnf gtqtytcnvd hkpsntkvdK tverkccvec
 251 ppcpappvag psvflfppkp kdtlmisrtp evtcvvvdvs hedpevqfnw
 301 yvdgvevhna ktkpreeqfn stfrvsvlt vvhqdwlngk eykckvsnkg
 351 lpapiektis ktkgqprepq vytlppsree mtknqvsltc lvkgfypsdi
 401 avewesngqp ennykttppm ldsdgsffly skltvdksrw qqgnvfscsv

451 mhealhnhyt qkslsislspgk

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises mature immunoglobulin heavy chain variable region 2.12.1 fx (amino acids 20-144 or SEQ ID NO: 33; SEQ ID NO: 34):

q vqlvesgggl vkpggslrls caasgftfsd yymswirgap gkglewvysi sssgstrdya
dsvkgrftis rdnaknslyl qmnsdraedt avyyccardgv ettfyyyyyg mdvwgqgttv tvss

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises an immunoglobulin light chain or mature fragment or variable region 2.12.1 fx (SEQ ID NO: 35) (in an embodiment of the invention, the leader sequence is underscored):

1 mdmrvpagll gllllwfpga rcdiqmtqsp sslsasvgdr vtitcrasqd
51 irrdlgwyqq kpgkapkrli yaasrlqsgv psrfsgsgsg teftltissl
101 qpedfatyye lqhnnyptrtf gqgkveikr tvaapsvfif ppsdeqlksg
151 tasvvcilnn fypreakvqw kvdnalqsgn sgesvteqds kdstyslsst
201 ltlskadyek hkvyacevth qglsspvtks fnrgec

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises mature immunoglobulin light chain variable region 2.12.1 fx (amino acids 23-130 of SEQ ID NO: 35; SEQ ID NO: 36):

diqmtqsp sslsasvgdr vtitcrasqd irrdlgwyqq kpgkapkrli yaasrlqsgv psrfsgsgsg
teftltissl qpedfatyye lqhnnyptrtf gqgkveikr

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises a humanized 7C10 immunoglobulin light chain variable region; version 1 (SEQ ID NO: 37):

1 divmtqspls lpvtpgepas iscrssqsiv hsnngntylqw ylkpqqspq
51 lliykvsnl ygvprfsgs gsgtdftlki srveaedvgv yycfqqshvp
101 wtfgqgkve ik

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises humanized 7C10 immunoglobulin light chain variable region; version 2 (SEQ ID NO: 38):

1 divmtqspls lpvtpgepas iscrssqsiv hsnngntylqw ylkpqqspq
51 lliykvsnl ygvprfsgs gsgtdftlki srveaedvgv yycfqqshvp
101 wtfgqgkve ik

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises a humanized 7C10 immunoglobulin heavy chain variable region; version 1 (SEQ ID NO: 39):

1 qvqlqesgpg lvkpsetlsl tctvsgysit ggylwnwirq ppgkglewmg
51 yisydgtnny kpslkdriti srdtsknqfs lklssvtaad tavyyccaryg
101 rvffdywgqg tlvtvss

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises the humanized 7C10 immunoglobulin heavy chain variable region; version 2 (SEQ ID NO: 40):

5 1 qvqlqesgpg lvkpsetls1 tctvsgysit ggylwnwirq ppgkglewig
 51 yisydgtnny kpslkdrvti srdtsknqfs lklssvtaad tavyycaryg
 101 rvffdywgqg tltvtvss

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises the humanized 7C10 immunoglobulin heavy chain variable region; version 3 (SEQ ID NO: 41):

 1 qvqlqesgpg lvkpsetls1 tctvsgysis ggylwnwirq ppgkglewig
 51 yisydgtnny kpslkdrvti svdtsknqfs lklssvtaad tavyycaryg
15 101 rvffdywgqg tltvtvss

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises A12 immunoglobulin heavy chain variable region (SEQ ID NO: 42):

 1 evqlvqsgae vkkpgssvkv sckasggtfs syaiswvrqa ppgglewmgg
20 51 iipifgtany aqkfqgrvti tadkststay melsslrsed tavyycarap
 101 lrflwestqd hyyyyymdvw gkgttvtvss

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises A12 immunoglobulin light chain variable region (SEQ ID NO: 43):

25 1 sseltqdpav svalgqtvri tcqgdsrlsy yaswyqqkpg qapvlviygk
 51 nnrpsgipdr fsgsssgnta sltitgaqae deadyycnsr dnsdnrlifg
 101 ggtkltvls

or

(SEQ ID NO: 105):

30 1 sseltqdpav svalgqtvri tcqgdsrlsy yatwyqqkpg qapilviyge
 51 nkrpsgipdr fsgsssgnta sltitgaqae deadyycksr dgsgqhlvfg
 101 ggtkltvlg

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises 1A immunoglobulin heavy chain variable region (SEQ ID NO: 44):

35 1 evqlvqsggg lvhpggslrl scagsgftfr nyamywvrqa ppgkglewvsa
 51 igsgggtyya dsvkgrftis rdnaknsllyl qmnsdraedm avyyicarapn
 101 wgsdafdiwg qgtmvtvss

;optionally including one or more of the following mutations: R30, S30, N31, S31, Y94, H94, D104, E104.

40 In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises 1A immunoglobulin light chain variable region (SEQ ID NO: 45):

 1 diqmtqspss lsasvgdrvt itcrasqgis swlawyqqkp ekapksliya
 51 asslqsgvps rfsqsgsgtd ftltisslqp edfatyyccq ynsypptfpg
45 101 gtkvdik

;optionally including one or more of the following mutations: P96, I96, P100, Q100, R103, K103, V104, L104, D105, E105

In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises single chain antibody (fv) 8A1 (SEQ ID NO: 46):

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5  1  evqlvqsgae vkkpgeslti sckgpgynff nywigwvrqm pgkglewmgi
51  iyptdsdtry spsfggqvti svdkstistay lqwsslkasd tamyycarsi
101 rycpggrcys gyygmdvwgq gtmvtvssgg gsgsgsgsgg ggsseltqdp
151 avsvalgqtv ritcqqgdsir syyaswyqqk pgqapvlviy gknnrpsgip
201 drfsgsssgn tasltitgaq aedeaddyen srdssgnhvv fgggtkltlv
10 251 g

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In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises single chain antibody (fv) 9A2 (SEQ ID NO: 47):

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15 1  qvqlvqsgae vrkpgasvkv scktsgytfr nydinwvrqa pggglewmgr
51  isghygnthd aqkfgrftm tkdtstistay melrsltfdd tavyycarsq
101 wnvdywgrgt lvtvssgggg sggsgsgsgg salnfmltqp hvsespqgt
151 vtisctrssg siasnyvqwy qqrpgssptt vifednrps gvpdrfsgsi
201 dtssnsaslt isglktedea dyycqsfdst nlvvfgggtk vtvlg

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In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises single chain antibody (fv) 11A4 (SEQ ID NO: 48):

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25 1  evqllesggg lvqpgrslrl scaasgftfs syamswvrqa pgkglewvsa
51  isgsggstyy adsvkgrfti srdnsntly lqmnslraed tavyycassp
101 yssrwsfddp wgqgtmvtvs sggsgsgsgg sggsgsalsy eltqppsvsv
25 151 spgqtatitc sgddlgnkyv swyqqkpgqs pvlviyqdtk rpsgiperfs
201 gsnsgniatl tisgtqavde adyycqvwtd gtvvfgggtk ltvlg

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In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises single chain antibody (fv) 7A4 (SEQ ID NO: 49):

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30 1  evqlvqsgae vkkpgeslti sckgsgynff nywigwvrqm pgkdlewmg
51  iyptdsdtry spsfggqvti svdkstistay lqwsslkasd tamyycarsi
101 rycpggrcys gyygmdvwgq gtmvtvssgg gsgsgsgsgg ggsseltqdp
151 avsvalgqtv ritcrgdsir nyyaswyqqk pgqapvlviy gknnrpsgip
201 drfsgsssgn tasltitgaq aedeaddyen srdssgnhmv fgggtkltlv
35 251 g

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In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises single chain antibody (fv) 11A1 (SEQ ID NO: 50):

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40 1  evqlvesggg vvqpgrslrl scaasgftfs dfamhwvrqi pgkglewls
51  lrhdgstayy agsvkgrfti srdnsrntvy lqmnslraed tatyycvtgs
101 gssgphafpv wgkgtlvtvs sggsgsgsgg sggsgsalsy vltqppsasg
151 tpgqrvtisc sgnsnigty tvnwfqqlpg tapklliysn nqrpsgvpdr
201 fsgsksgtsa slaisglqse deaddycaaw ddslnpgvfg ggktvltvlg

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In an embodiment of the invention, an anti-IGF1R antibody of the invention comprises single chain antibody (fv) 7A6 (SEQ ID NO: 51)

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45 1  evqlvqsgae vkkpgeslti sckgsgynff nywigwvrqm pgkglewmgi
51  iyptdsdtry spsfggqvti svdkstistay lqwsslkasd tamyycarsi

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101 rycpgggrcys gyygmdvwgq gtlvtvssgg ggsggggsgg ggsseltqdp
 151 avsvalgqtv ritcqqgdsir syytwnwfqqk pgqapllvvy aknkrpsgip
 201 drfsgsssgn tasltitgaq aeadeayycn srdssgnhvv fgggtklvtl
 251 g

5

In an embodiment of the invention, an anti-IGF1R antibody or an antigen-binding fragment thereof (e.g., a heavy chain or light chain immunoglobulin) of the invention comprises one or more complementarity determining regions (CDR) selected from the group consisting of:

- 10 sywmh (SEQ ID NO: 52);
 einpsngrtrnynefkfr (SEQ ID NO: 53);
 grpdyygsskwyfdv (SEQ ID NO: 54);
 rssqsivhsnvnstyle (SEQ ID NO: 55);
 kvsnrfs (SEQ ID NO: 56); and
 15 fggshvppt (SEQ ID NO: 57).

In an embodiment of the invention, an anti-IGF1R antibody or an antigen-binding fragment thereof of the invention comprises a heavy chain immunoglobulin variable region selected from the group consisting of :

- 20 1 qvqlvqsgae vvkpgasvkl sckasgytft sywmhvwkqr pgqglewige
 51 inpsngrtrny nqkfqqkatl tvdkssstay mqlssltsed savyyfargr
 101 pdyygsskwy fdvwgqgttv tvs
 (SEQ ID NO: 58);

- 25 1 qvqlqqsgae lvkpgasvkl sckasgytft sylmhvwikqr pgrglewigr
 51 idpnnvvtkf nekfkskatl tvdkpsstay melssltsed savyycarya
 101 ycrpmdywgq gttvtvss
 (SEQ ID NO: 59);

- 30 1 qvqlqqsgae lvkpgasvkl sckasgytft sywmhvwkqr pgqglewige
 51 inpsngrtrny nekfkkrkatl tvdkssstay mqlssltsed savyyfargr
 101 pdyygsskwy fdvwgagttv tvs
 (SEQ ID NO: 60);

- 35 1 qvqlqqsgae lmkpgasvki sckatgytfs sfwiewvkqr pghglewige
 51 ilpgsggthy nekfkkgatf tadkssntay mqlssltsed savyycargh
 101 syfydygdyw ggtsvtvss
 (SEQ ID NO: 61);

- 40 1 qvqlqqpgsv lvrpgasvkl sckasgytft sswihwakqr pgqglewige
 51 ihpnsgrtny nekfkkgatl tvdtssstay vdlssltsed savyycarwr
 101 ygspyyfdyw gggttltvss
 (SEQ ID NO: 62);

- 45 1 qvqlqqpgae lvkpgasvkl sckasgytft sywmhvwkqr pgrglewigr
 51 idpnsngtky nekfkskatl tvdkpsstay mqlssltsed savyycaryd
 101 yygssyfdyw gggttltvss

(SEQ ID NO: 63);

5 1 qvqlvqsgae vvkpgasvkl sckasgytft sywmhvwkqr pgqglewige
 51 inpsngrtny nqkfqqkatl tvdkssstay mqlssltsed savyyfargr
 101 pdyygsskwy fdvwgqgttv tvs

(SEQ ID NO: 64);

10 1 qvqlqqsgae lvkpgasvkl sckasgytft sywmhvwkqr pgqglewige
 51 inpsngrtny nekfkrrkatl tvdkssstay mqlssltsed savyyfargr
 101 pdyygsskwy fdvwgagttv tvss

(SEQ ID NO: 65);

15 1 qvqlvqsgae vvkpgasvkl sckasgytft sywmhvwkqr pgqglewige
 51 inpsngrtny nqkfqqkatl tvdkssstay mqlssltsed savyyfargr
 101 pdyygsskwy fdvwgqgttv tvss

(SEQ ID NO: 66);

20 1 qvqlqqsgae lvkpgasvkl sckasgytft sywmhvwkqr pgrglewigr
 51 idpnsngtky nekfkrrkatl tvdkpsstay mqlssltsed savyyfargr
 101 yygssyfdyw gqgtttvtvss

(SEQ ID NO: 67);

25 1 qiqlqqsgpe lvrpgasvki sckasgytft dyvihvwkqr pgeglewigw
 51 iypgsgntky nekfkkgkatl tvdtssstay mqlssltsed savyfcargg
 101 kfamdywgqg tsvtvss

(SEQ ID NO: 68);

30 1 qvqlqqsgae lvkpgasvkl sckasgytft sywmhvwkqr pgqglewige
 51 inpsngrtny nekfkrrkatl tvdkssstay mqlssltsed savyyfargr
 101 pdyygsskwy fdvwgagttv tvss

(SEQ ID NO: 69);

35 1 qiqlqqsgpe lvkpgasvki sckasgytft dyvinwmkqk pgqglewigw
 51 idpnsngtky nekfkkgkatl tvdtssstay mqlssltsed tavyfcarek
 101 ttyyyamdyw gqgtsvtvsa

(SEQ ID NO: 70);

40 1 vqlqqsgael mkpgasvkis ckasgytfsd ywiewvkqrp ghglewigei
 51 lpgsgstnyh erfkgkatft adtssstaym qlnsltseds gvyycalhgy
 101 dfdgwgqgtt ltvss

(SEQ ID NO: 71); and

45 1 qvqllesgae lmkpgasvki sckatgytfs sfwiewvkqr pghglewige
 51 ilpgsggthy nekfkkgkatf tadkssntay mqlssltsed savyycargh
 101 syfydgdyw gqgtsvtvss

(SEQ ID NO: 72);

50 and/or a light chain immunoglobulin variable region selected from the group
 consisting of:

 1 dvlmtqipvs lpvslgdqas iscrssqiiv hnnngntylew ylaqkpgqspq
 51 lliykvsnrfs sgvpdrfsgs gsgtdftlki srveaedlgv yycfqqshvp
 101 ftfgsgtkle ikr

(SEQ ID NO: 73);

55

1 dvlmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspk
51 lliykvsnrfg sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 74);

1 dvlmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspr
51 lliykvsnrfg sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 75);

1 dvlmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspk
51 lliykvsnrfg sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 76);

1 dvlmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspr
51 lliykvsnrfg sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 77);

1 dvlmtqtpls lpvslgdqas iscrssqxiv hsnvntylew ylkpggqspk
51 lliykvsnrfg sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgshvp
101 xtfgggkcle ikr
(SEQ ID NO: 78);

1 dvvmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspk
51 lliykvsnrfg sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 79);

1 dvvmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspr
51 lliykvsnrfg sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 80);

1 dvlmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspr
51 lliykvsnrfg sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 81);

1 dvlmtqipvs lpvslgdqas iscrssqiiv hsnvntylew ylkpggqspq
51 lliykvsnrfg sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgshvp
101 ftfgsggkcle ikr
(SEQ ID NO: 82);

1 dvlmtqtpls lpvslgdqas iscrfsqsiv hsnvntylew ylksggqspk
51 lliykvsnrfg sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgshvp
101 rtfgggkcle ikr
(SEQ ID NO: 83);

1 dvlmtqtpls lpvslgdqas iscrssqsiv hsnvntylew ylkpggqspk
51 lliykvsnrfg sgvpdrfsgs gsgtdftlri srveaedlgi yycfqqgshvp
101 ptfggggkcle ikr
(SEQ ID NO: 84);

1 dvvmtqtpls lpvslgdpas iscrssqsiv hsnvntylew ylkpggqspk

51 lliykvsnrfr sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 85);

5 1 elvmtqtpls lpvslgdqas iscrssqstiv hsnngdtyldw flqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 86);

10 1 dvlmtqtpls lpvslgdqas iscrssqsiv hsnvntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 87);

15 1 dvvmtqtpls lpvslgdqas iscrssqsiv hsnvntylew ylqkpggqspr
 51 lliykvsnrfr sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 88);

20 1 dvlmtqtpls lpvslgdqas iscrssqsiv hstgntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgshap
 101 rtfggggkcle ikr
 (SEQ ID NO: 89);

25 1 dvlmtqtpls lpvslgdqas isckssqsiv hssgntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgship
 101 ftfgsgtkcle ikr
 (SEQ ID NO: 90);

30 1 dieltqtpls lpvslgdqas iscrssqsiv hsnngntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgshvp
 101 ytfgggkcle ikr
 (SEQ ID NO: 91);

35 1 dvlmtqtpls lpvslgdqas iscrssqsiv hsnvntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gsgtdftlri srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 92);

40 1 dvvmtqtpls lpvslgdqas iscrssqsiv hsnvntylew ylqkpggqspr
 51 lliykvsnrfr sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 93);

45 1 dvlmtqtpls lpvslgdqas iscrssqsiv hsnvntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gsgtdftlri srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 94);

50 1 dvvmtqtpls lpvslgdqas iscrssqsiv hsnvntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gagtdftlri srveaedlgi yycfqqgshvp
 101 ptfggggkcle ikr
 (SEQ ID NO: 95);

55 1 dvlmtqtpls lpvslgdqas iscrsnqtil lsdgntylew ylqkpggqspk
 51 lliykvsnrfr sgvpdrfsgs gsgtdftlki srveaedlgi yycfqqgshvp

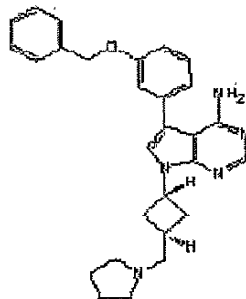
101 ptfggggtklee ikr
(SEQ ID NO: 96);

1 dvlmtqtpls lpvslgdqas iscrssqtiv hsnngntylew ylkpggqspk
5 51 lliykvtmr sgvpdrfsgs gsgtdftlki srveaedlgv yycfaggthap
101 ytfggggtklee ikr
(SEQ ID NO: 97); and

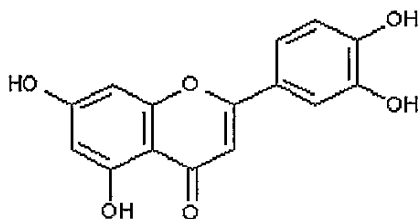
1 dvlmtqtpls lpvslgdqas iscrssqsiv hsnngntylew ylkpggqspk
10 51 lliysissrf sgvpdrfsgs gsgtdftlki srveaedlgv yycfaggshvp
101 ytfggggtklee ikr
(SEQ ID NO: 98).

The scope of the present invention includes methods wherein a patient is
15 administered an anti-insulin-like growth factor receptor-1 (IGF1R) antibody wherein the
variable region of the antibody is linked to any immunoglobulin constant region. In an
embodiment, the light chain variable region is linked to a κ chain constant region. In an
embodiment, the heavy chain variable region is linked to a γ 1, γ 2, γ 3 or γ 4 chain constant
region. Any of the immunoglobulin variable regions set forth herein, in embodiments of
20 the invention, can be linked to any of the foregoing constant regions.

In an embodiment of the invention, an IGF1R inhibitory agent that can be
administered to a patient in a method according to the invention is AEW-541 (NVP-AEW-
541; NVP-AEW-541-NX-7):



(Novartis; East Hanover, NJ; see WO 2002/92599); or



25

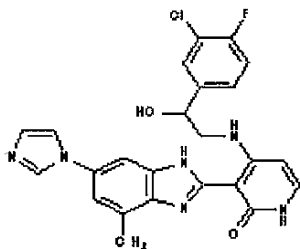
(WO 2003/39538).

In an embodiment of the invention, an IGF1R inhibitory agent that can be
administered to a patient in a method according to the invention is any IGF1R anti-sense
nucleic acid. For example, in an embodiment, the anti-sense IGF1R nucleic acid is ATL-

1101 (Antisense Therapeutics Ltd; Australia). In an embodiment, the IGF1R anti-sense nucleic acid comprises any of the following nucleotide sequences: 5'-ATCTCTCCGCTTCCTTTC-3' (SEQ ID NO: 99), 5'-ATCTCTCCGCTTCCTTTC-3' (SEQ ID NO: 100), 5'-ATCTCTCCGCTTCCTTTC-3' (SEQ ID NO: 101) or any IGF1R antisense nucleic acid set forth in any of US Published Patent Application No. US20030096769; Published International Application No. WO 2003/100059; Fogarty *et al.*, Antisense Nucleic Acid Drug Dev. 2002 Dec;12(6):369-77; White *et al.*, J Invest Dermatol. 2002 Jun;118(6):1003-7; White *et al.*, Antisense Nucleic Acid Drug Dev. 2000 Jun;10(3):195-203; or Wraight *et al.*, Nat Biotechnol. 2000 May;18(5):521-6.

In an embodiment of the invention, an IGF1R inhibitory agent that can be administered to a patient in a method according to the invention is an anti-IGF-I or II antibody; for example, any antibody disclosed in WO 2003/93317 or EP00492552.

The scope of the present invention includes any kinase inhibitor compound set forth in published international applications WO 2004/030627 or WO 2004/030625. In an embodiment, the kinase inhibitor is (\pm)-4-[2-(3-chloro-4-fluoro-phenyl)-2-hydroxy-ethylamino]-3-[6-(imidazol-1-yl)-4-methyl-1H-benzimidazol-2-yl]-1H-pyridin-2-one:



(optionally in combination with paclitaxel or with

cetuximab).

In an embodiment of the invention, the IGR1R inhibitory agent is a soluble fragment of IGF1R (e.g., amino acids 30-902 of IGF1R) or siRNA (small interfering RNA) against IGF-1R.

In an embodiment, IGF1R comprises the amino acid sequence set forth under Genbank Accession No.: XM_052648 or NM_000612.

The present invention also includes embodiments wherein the patient receives both an IGF1R inhibitory agent in association with one or more other anti-cancer agents, including, but not limited to paclitaxel, thalidomide, docetaxel, gefitinib, temozolomide, lonafarnib, tipifarnib, letrozole, doxorubicin, cis-platin, oxaliplatin, camptothecin, topotecan, etoposide, vincristine, vinblastine, raloxifene, gemcitabine, retinoic acid, tamoxifen, trastuzumab, cetuximab or octreotide; or anti-cancer therapeutic procedures

including, but not limited to, surgical tumorectomy or anti-cancer radiation therapy. The present invention further includes embodiment wherein two or more IGF1R inhibitory agents are administered in association with one another.

The term "in association" indicates that the components of the combinations of the invention can be formulated into a single composition for simultaneous delivery or formulated separately into two or more compositions (*e.g.*, a kit). Furthermore, each component of a combination of the invention can be administered to a subject at a different time than when the other component is administered; for example, each administration may be given non-simultaneously at several intervals over a given period of time. Moreover, the separate components may be administered to a subject by the same or by a different route (*e.g.*, orally, intravenously, intratumorally).

Generation of Antibodies

Any suitable method can be used to elicit an antibody with the desired biologic properties to inhibit IGF1R. It is desirable to prepare monoclonal antibodies (mAbs) from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, *e.g.*, Stites, *et al.* (eds.) BASIC AND CLINICAL IMMUNOLOGY (4th ed.) Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) ANTIBODIES: A LABORATORY MANUAL CSH Press; Goding (1986) MONOCLONAL ANTIBODIES: PRINCIPLES AND PRACTICE (2d ed.) Academic Press, New York, NY. Thus, monoclonal antibodies may be obtained by a variety of techniques familiar to researchers skilled in the art. Typically, spleen cells from an animal immunized with a desired antigen are immortalized, commonly by fusion with a myeloma cell. See Kohler and Milstein (1976) Eur. J. Immunol. 6:511-519. Alternative methods of immortalization include transformation with Epstein Barr Virus, oncogenes, or retroviruses, or other methods known in the art. See, *e.g.*, Doyle, *et al.* (eds. 1994 and periodic supplements) CELL AND TISSUE CULTURE: LABORATORY PROCEDURES, John Wiley and Sons, New York, NY. Colonies arising from single immortalized cells are screened for production of antibodies of the desired specificity and affinity for the antigen, and yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host. Alternatively, one may isolate DNA sequences which encode a monoclonal antibody or a binding fragment thereof by screening a DNA library from human B cells according, *e.g.*, to the general

protocol outlined by Huse, *et al.* (1989) Science 246:1275-1281. Modified antibodies can be generated, for example, by introducing mutations in DNA encoding an immunoglobulin chain, for example, by use of conventional recombinant biological techniques.

Other suitable techniques involve selection of libraries of antibodies in phage or similar vectors. See, *e.g.*, Huse *et al.*, Science 246:1275-1281 (1989); and Ward *et al.*, Nature 341:544-546 (1989). The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant immunoglobulins may be produced, see Cabilly U.S. Patent No. 4,816,567; and Queen *et al.* (1989) Proc. Nat'l Acad. Sci. USA 86:10029-10033; or made in transgenic mice, see Mendez *et al.* (1997) Nature Genetics 15:146-156. Further methods for producing chimeric, humanized and human antibodies are well known in the art. See, *e.g.*, U.S. Pat. No. 5,530,101, issued to Queen *et al.*, U.S. Pat. No. 5,225,539, issued to Winter *et al.*, U. S. Pat. Nos. 4,816,397 issued to Boss *et al.*, all of which are incorporated by reference in their entirety.

Tumor analysis

The methods of the present method comprise determining whether tumor cells comprising one or more of the following characteristics:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II expression;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) expression of IGF1R.

Tumor cells can be assayed to determine whether any of these characteristics are present by any of several methods commonly known in the art. In an embodiment, IRS-1 or IGF1R tyrosine phosphorylation can be determine by western blot analysis with an anti-

phosphotyrosine antibody. For example, anti-phosphotyrosine antibodies PY20, PT66 and P-Try-100 are commercially available from PerkinElmer Life and Analytical Sciences, Inc. (Boston, MA); and anti-phosphotyrosine antibody 4G10 is commercially available from Upstate Cell Signaling Solutions (Waltham, MA). Western blot analysis is a conventional method that is well known in the art. In an embodiment, IRS-1 or IGF1R tyrosine phosphorylation can be determined by an Enzyme linked immunosorbent assay (ELISA) or immunoprecipitation. In an embodiment, expression of IGF1R or IGF-II by tumor cells can, similarly, be determined by western blot analysis, immunoprecipitation or by ELISA. Any of several anti-IGF1R antibodies known in the art, for example, as described herein, can be used.

Many references are available to provide guidance in applying the above techniques (Kohler *et al.*, Hybridoma Techniques (Cold Spring Harbor Laboratory, New York, 1980); Tijssen, Practice and Theory of Enzyme Immunoassays (Elsevier, Amsterdam, 1985); Campbell, Monoclonal Antibody Technology (Elsevier, Amsterdam, 1984); Hurrell, Monoclonal Hybridoma Antibodies: Techniques and Applications (CRC Press, Boca Raton, FL, 1982); Zola, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, Inc., 1987)).

In an embodiment of the invention, IGF-II expression by a tumor cell can be determined by *IGF-II* RNA detection. In an embodiment of the invention, IGF-II RNA is determined by northern blot analysis. Northern blot analysis is a conventional technique well known in the art and is described, for example, in Molecular Cloning, a Laboratory Manual, second edition, 1989, Sambrook, Fritsch, Maniatis, Cold Spring Harbor Press, 10 Skyline Drive, Plainview, NY 11803-2500.

Dosage

In an embodiment, an IGF1R inhibitory agent is administered to a patient at a "therapeutically effective dosage" or "therapeutically effective amount" which preferably inhibits a disease or condition (e.g., tumor growth) to any extent-preferably by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80%-100% relative to untreated subjects. In an embodiment of the invention, the term "therapeutically effective amount" or "therapeutically effective dosage" means that amount or dosage of an IGF1R inhibitory agent (e.g., an anti-IGF1R antibody or antigen-binding fragment thereof) that will elicit a biological or medical response of a tissue, system, subject or host that is being sought by

the administrator (such as a researcher, doctor or veterinarian) which includes any measurable alleviation of the signs, symptoms and/or clinical indicia of cancer (e.g., tumor growth) and/or the prevention, slowing or halting of progression or metastasis of cancer to any degree. The ability of an IGF1R inhibitory agent to inhibit cancer can be evaluated in an animal model system predictive of efficacy in human tumors. Alternatively, efficacy can be evaluated by examining the ability of a treatment of the invention or any component thereof to inhibit tumor cell growth *in vitro* by assays well-known to the skilled practitioner. One of ordinary skill in the art would be able to determine such amounts based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected.

A clinician may use any of several methods known in the art to measure the effectiveness of a particular dosage scheme of an IGF1R inhibitory agent. For example, tumor size can be determined in a non-invasive route, such as by X-ray, positron emission tomography (PET) scan, computed tomography (CT) scan or magnetic resonance imaging (MRI).

A cancer or a tumor cell is "responsive" to an IGF1R inhibitory agent if the agent can provide any measurable alleviation of the signs, symptoms and/or clinical indicia of cancer (e.g., tumor growth) and/or the prevention, slowing or halting of progression or metastasis of cancer to any degree.

Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a dose may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of an IGF1R inhibitory agent employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. The effectiveness of a given dose or treatment regimen of IGF1R inhibitory agent can be determined, for example, by determining whether a tumor being treated in the subject shrinks or ceases to grow.

In an embodiment of the invention, administration of IGF1R inhibitory agent is by injection proximal to the site of the target (e.g., tumor). In an embodiment, a therapeutically effective daily dose of IGF1R inhibitory agent or pharmaceutical composition thereof is administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day. In an embodiment, a “therapeutically effective” dosage of any anti-IGFR antibody (e.g., 19D12/15H12 LCF/HCA) is in the range of about 3 mg/kg (body weight) to about 20 mg/kg (e.g., 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg or 20 mg/kg) per day. In an embodiment, a “therapeutically effective dosage” of a chemotherapeutic agent (e.g., an IGF1R inhibitory agent) is whenever possible as set forth in the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)) which is herein incorporated by reference. For example, in an embodiment of the invention, a therapeutically effective dosage of NVP-ADW-742 is about 1 mg/kg/day to about 50 mg/kg/day (e.g., 5 mg/kg/day, 10 mg/kg/day, 15 mg/kg/day, 20 mg/kg/day, 25 mg/kg/day, 30 mg/kg/day, 35 mg/kg/day, 40 mg/kg/day, 45 mg/kg/day).

Therapeutic Methods and Administration

An IGF1R inhibitory agent can be used to inhibit or reduce the growth or proliferation of any cell, such as a malignant cell, either *in vitro* (e.g., in cell culture) or *in vivo* (e.g., within the body of a subject suffering from a disease mediated by elevated expression or activity of IGF1R or by elevated expression of its ligand (e.g., IGF-I or IGF-II)). Such inhibition or reduction of growth or proliferation of a cell can be achieved by contacting the cell with the IGF1R inhibitory agent.

In an embodiment, an IGF1R inhibitory agent is for treating cancer in a patient that is characterized by one or more of the following characteristics: (i) IRS-1 phosphorylation on tyrosine 896; (ii) IRS-1 phosphorylation on tyrosine 612; (iii) IRS-1 phosphorylation on any tyrosine; (iv) IGF-II expression; (v) IGF1R phosphorylation on any tyrosine; or (vi) expression of IGF1R. For example, in an embodiment, the cancer is bladder cancer, Wilm's cancer, bone cancer, prostate cancer, lung cancer, endometrial cancer, multiple myeloma, non-small cell lung cancer (NSCLC), colon cancer, rectal cancer, colorectal cancer, breast cancer (estrogen receptor⁺ or estrogen receptor⁻), cervical cancer, synovial sarcoma, ovarian cancer, pancreatic cancer, neuroblastoma, rhabdomyosarcoma, osteosarcoma, diarrhea associated with metastatic carcinoid or

vasoactive intestinal peptide secreting tumor (e.g., VIPoma or Werner-Morrison syndrome).

In an embodiment, it is initially determined if a prospective patient to be treated with an IGF1R inhibitory agent suffers from a variety of cancer that is commonly known to exhibit one of the following characteristics: (i) IRS-1 phosphorylation on tyrosine 896; (ii) IRS-1 phosphorylation on tyrosine 612; (iii) IRS-1 phosphorylation on any tyrosine; (iv) IGF-II expression; (v) IGF1R phosphorylation on any tyrosine; or (vi) expression of IGF1R. If the patient is determined to suffer from a cancer known to be characterized by one or more of the 6 characteristics set forth above, the patient is selected for treatment with an IGF1R inhibitory agent. A tumor type may be known to comprise any of the listed characteristics, for example, if such is established in scientific literature (e.g., periodic journals or textbooks) or if such is commonly known in the art by practitioners of ordinary skill or if such a characteristic has ever been observed in one or more patients or tumors, or if such can reasonably be inferred from experimental data (e.g., *in vitro* or *in vivo* data including animal data).

In an embodiment of the invention, a prospective patient's individual tumor is analyzed and it is determined whether the tumor exhibits one of more of the 6 characteristics: (i) IRS-1 phosphorylation on tyrosine 896; (ii) IRS-1 phosphorylation on tyrosine 612; (iii) IRS-1 phosphorylation on any tyrosine; (iv) IGF-II expression; (v) IGF1R phosphorylation on any tyrosine; or (vi) expression of IGF1R. In this embodiment, if the patient's tumor is determined to be characterized by one or more of the 6 characteristics set forth above, the patient is selected for treatment with an IGF1R inhibitory agent. In an embodiment, it is first determined whether the patient's tumor expresses the characteristic (i) IRS-1 phosphorylation on tyrosine 896 or (ii) IRS-1 phosphorylation on tyrosine 612; then, if such a characteristic is identified, it is determined whether the tumor comprises the characteristic (iv) IGF-II expression; if the patient's tumor is determined to express characteristic (i) or (ii) and characteristic (iv), then the patient is selected for treatment with an IGF1R inhibitory agent.

The cells from a particular patient's tumor can be obtained surgically, for example, by surgical biopsy. For example, a tumor biopsy can be taken by endoscopic biopsy, excisional or incisional biopsy or fine needle aspiration (FNA) biopsy.

The term "patient" or "subject" includes any organism, preferably an animal, more preferably a mammal (e.g., rat, mouse, dog, cat, rabbit) and most preferably a human.

As stated above, in an embodiment of the invention, where possible, an IGF1R inhibitory agent is administered to a subject in accordance with the Physicians' Desk Reference 2003 (Thomson Healthcare; 57th edition (November 1, 2002)) or as set forth herein.

5 An IGF1R inhibitory agent can be administered by an invasive route such as by injection (see above). Administration by a non-invasive route (e.g., orally; for example, in a pill, capsule or tablet) is also within the scope of the present invention. In an embodiment of the invention, an anti-IGF1R antibody (e.g., 15H12/19D12 LCF/HCA), or pharmaceutical composition thereof, is administered intravenously, subcutaneously,
10 intramuscularly, intraarterially or intratumorally.

An IGF1R inhibitory agent can be administered with medical devices known in the art. For example, a pharmaceutical composition of the invention can be administered by injection with a hypodermic needle.

The pharmaceutical compositions of the invention may also be administered with a
15 needleless hypodermic injection device; such as the devices disclosed in U.S. Patent Nos. 6,620,135; 6,096,002; 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824 or 4,596,556.

Examples of well-known implants and modules for administering pharmaceutical compositions include: U.S. Patent No. 4,487,603, which discloses an implantable micro-
20 infusion pump for dispensing medication at a controlled rate; U.S. Patent No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Patent No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Patent No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments. Many other such
25 implants, delivery systems, and modules are well known to those skilled in the art.

Pharmaceutical Compositions

An IGF1R inhibitory agent can be incorporated into a pharmaceutical composition, along with a pharmaceutically acceptable carrier, suitable for administration to a subject *in*
30 *vivo*. The scope of the present invention includes pharmaceutical compositions which are suitable to be administered to a subject by any route including, for example, oral, ocular, topical, pulmonary (inhalation), intratumoral injection, intravenous injection, subcutaneous injection or intramuscular injection.

For general information concerning formulations, see, e.g., Gilman, *et al.*, (eds.) (1990), The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; A. Gennaro (ed.), Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.; Avis, *et al.*, (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, New York; Lieberman, *et al.*, (eds.) (1990) Pharmaceutical Dosage Forms: Tablets Dekker, New York; and Lieberman, *et al.*, (eds.) (1990), Pharmaceutical Dosage Forms: Disperse Systems Dekker, New York, Kenneth A. Walters (ed.) (2002) Dermatological and Transdermal Formulations (Drugs and the Pharmaceutical Sciences), Vol 119, Marcel Dekker.

Pharmaceutically acceptable carriers are conventional and very well known in the art. Examples include aqueous and nonaqueous carriers, stabilizers, antioxidants, solvents, dispersion media, coatings, antimicrobial agents, buffers, serum proteins, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for injection into a subject's body.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Examples of pharmaceutically-acceptable antioxidants include: water soluble antioxidants such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; and oil-soluble antioxidants such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Prevention of the presence of microorganisms may be ensured both by sterilization procedures, and by the inclusion of various antimicrobial agents such as EDTA, EGTA, paraben, chlorobutanol, phenol sorbic acid, and the like.

Suitable buffers which may be included in the pharmaceutical compositions of the invention include L-histidine based buffers, phosphate based buffers (e.g., phosphate buffered saline, pH \approx 7), sorbate based buffers or glycine-based buffers.

Serum proteins which may be included in the pharmaceutical compositions of the invention may include human serum albumin.

Isotonic agents, such as sugars (*e.g.*, sucrose), ethanol, polyalcohols (*e.g.*, glycerol, propylene glycol, liquid polyethylene glycol, mannitol or sorbitol), sodium citrate
5 or sodium chloride (*e.g.*, buffered saline) may also be included in the pharmaceutical compositions of the invention. In an embodiment of the invention, the sugar, for example, glucose or sucrose is present at a high concentration (*e.g.*, about 10-100 mg/ml, *e.g.*, 50mg/ml, 60 mg/ml or 70 mg/ml).

Prolonged absorption of an injectable pharmaceutical form may be brought about
10 by the inclusion of agents which delay absorption such as aluminum monostearate and/or gelatin.

Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils.

Pharmaceutically acceptable carriers include sterile aqueous solutions or
15 dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art.

Sterile injectable solutions comprising an anti-IGF1R antibody can be prepared by incorporating the antibody or antigen-binding fragment thereof in the required amount in
20 an appropriate solvent, optionally with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the antibody into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred
25 methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional, desired ingredient from a previously sterile-filtered solution thereof.

In an embodiment of the invention, an anti-IGF1R antibody of the invention is in a pharmaceutical formulation comprising a therapeutically effective amount of said
30 antibody, a buffer and sucrose. For example, in an embodiment of the invention, the buffer is any one of phosphate buffer, citrate buffer, histidine buffer, glycine buffer or acetate buffer. The pharmaceutical formulation can be within any suitable pH range. In an embodiment of the invention, the pH is 5.0, 5.5, 6.0, 7.5, or between about 5.5 and about 6 or between about 5 and about 7.

An IGF1R inhibitory agent including an anti-IGF1R antibody or antigen-binding fragment thereof can be orally administered. Pharmaceutical compositions for oral administration may contain, in addition to the binding composition, additives such as starch (*e.g.*, potato, maize or wheat starch or cellulose), starch derivatives (*e.g.*,
5 microcrystalline cellulose or silica), sugars (*e.g.*, lactose), talc, stearate, magnesium carbonate or calcium phosphate. In order to ensure that oral compositions comprising an antibody or antigen-binding fragment of the invention are well tolerated by the patient's digestive system, mucus formers or resins may be included. It may also be desirable to improve tolerance by formulating the antibody or antigen-binding fragment in a capsule
10 which is insoluble in the gastric juices. An exemplary pharmaceutical composition of this invention in the form of a capsule is prepared by filling a standard two-piece hard gelatin capsule with the antibody or antigen-binding fragment of the invention in powdered form, lactose, talc and magnesium stearate. Oral administration of immunoglobulins has been described (Foster, *et al.*, (2001) Cochrane Database System rev. 3:CD001816)

15 An IGF1R inhibitory agent may also be included in a pharmaceutical composition for topical administration. Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site where treatment is required, such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

20 Drops may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving an IGF1R inhibitory agent in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration.

Lotions according to the present invention include those suitable for application to
25 the skin or eye. An eye lotion may comprise a sterile, aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

30 Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing an IGF1R inhibitory agent in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft

or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surface active such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

An IGF1R inhibitory agent may also be administered by inhalation. A suitable pharmaceutical composition for inhalation may be an aerosol. An exemplary pharmaceutical composition for inhalation of an antibody or antigen-binding fragment of the invention may include: an aerosol container with a capacity of 15-20 ml comprising the antibody or antigen-binding fragment of the invention, a lubricating agent, such as polysorbate 85 or oleic acid, dispersed in a propellant, such as freon, preferably in a combination of 1,2-dichlorotetrafluoroethane and difluorochloromethane. Preferably, the composition is in an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

Kits and Articles of Manufacture

Kits and articles of manufacture of the present invention include an IGF1R inhibitory agent, preferably combined with a pharmaceutically acceptable carrier, in a pharmaceutical formulation, more preferably in a pharmaceutical dosage form such as a pill, a powder, an injectable liquid, a tablet, dispersible granules, a capsule, a cachet or a suppository. See for example, Gilman *et al.* (eds.) (1990), *The Pharmacological Bases of Therapeutics*, 8th Ed., Pergamon Press; and Remington's *Pharmaceutical Sciences*, supra, Easton, Penn.; Avis *et al.* (eds.) (1993) *Pharmaceutical Dosage Forms: Parenteral Medications* Dekker, New York; Lieberman *et al.* (eds.) (1990) *Pharmaceutical Dosage Forms: Tablets* Dekker, New York; and Lieberman *et al.* (eds.) (1990), *Pharmaceutical Dosage Forms: Disperse Systems* Dekker, New York.

The kits and articles of manufacture of the present invention also include information, for example in the form of a package insert or label, indicating that the target of the IGF1R inhibitory agent is IGF1R. The term "target" indicates that the agent reduces or inhibits ligand binding, kinase activity, expression or any other biological activity of

IGF1R in any way. The insert or label may take any form, such as paper or on electronic media such as a magnetically recorded medium (e.g., floppy disk) or a CD-ROM.

The label or insert may also include other information concerning the pharmaceutical compositions and dosage forms in the kit or article of manufacture.

5 Generally, such information aids patients and physicians in using the enclosed pharmaceutical compositions and dosage forms effectively and safely. For example, the following information regarding the IGF1R inhibitory agent may be supplied in the insert: pharmacokinetics, pharmacodynamics, clinical studies, efficacy parameters, indications and usage, contraindications, warnings, precautions, adverse reactions, overdose,
10 proper dosage and administration, how supplied, proper storage conditions, references and patent information.

Examples

This section is intended to further describe the present invention and should not be
15 construed to further limit the invention. Any composition or method set forth herein comprises part of the present invention.

In this example, the level of phosphorylation of IRS-1 in human lung tumor tissue was compared to that of normal tissue samples and found to be higher in tumor cells than in normal cells. Also, the *in vivo* efficacy of the anti-IGF1R antibody 19D12/15H12
20 LCF/HCA was correlated with the ability of the IGF-1 to cause IRS-1 phosphorylation. In addition, the level of *IGF-II* mRNA expression was evaluated in 56 different normal and cancerous ovarian and colorectal tissue samples and found to be high in several samples of tumor tissue.

Tumor lysate preparation. Tumor tissues were first weighed and pulverized into
25 fine powder with a pre-chilled pulverizer on dry ice. Tumor powders were transferred into a tube, and 4.5x volume of the buffer A (*i.e.*, 450 ul buffer A per 100 mg tissue) was added. The samples were sonicated for 30 seconds, 0.5x volume of buffer B (*i.e.*, add 50 ul buffer B per 100 mg tissue powder) was added, and samples were spun for 13,000 rpm for 20 min at 4°C after incubation on ice for 30 min. Supernatants were collected and
30 protein concentrations of the lysates were determined by Bio-Rad assay.

Buffer A: 50 mM Hepes, pH 7.4, 150 mM NaCl, 5% Glycerol, 1.5 mM MgCl₂, 2 mM Sodium Vanadate, 5 mM NaF, Protease inhibitors (2x concentrated C complete EDTA-

free from Roche-cat #. 1 873 580), Phosphatase inhibitor Cocktail 1 (Sigma p2850), Phosphatase inhibitor Cocktail 2 (Sigma p5726).

Buffer B: Buffer A plus 10% Triton -100

5

Cell culture lysate preparation. Cells were washed in PBS once, lysed in buffer containing 50 mM Hepes, pH7.4, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1.5 mM MgCl₂, 2 mM Na₃VO₄ and protease inhibitor cocktail (CompleteTM, Roche Diagnostics GmbH; Mannheim, Germany). Samples were spun for 13,000 rpm for 10 min at 4°C after
10 incubation on ice for 30 min. Supernatants were collected and protein concentrations of the lysates were determined by Bio-Rad assay.

Western analysis. Equal amounts of cell or tumor lysates were separated on a SDS-PAGE, transferred to nitrocellulose filters, probed with desired antibodies, and visualized by ECL (Amersham; Piscataway, NJ). Antibodies for detecting IGFR and IRS-1
15 were from Santa Cruz Biotechnology (Santa Cruz, CA). Antibodies against phospho-IRS1[pY896] and phospho-IRS1[pY612] were from Biosource (Camarillo, CA).

IGF-II protein measurement. Cells from various cell lines were seeded in T-175 plates in medium containing 10% FBS. After cells were attached, medium was changed to serum free medium. Medium was collected, all debris was spun down, and the
20 supernatants were lyophilized. Cells on the plates were trypsinized and counted. Water was added to each lyophilized supernatant sample (1 ml/2x10⁷ cells). IGF-II was measured using the IGF-II ELISA kit from DSL (DSL-10-2600). IGF-II amounts were determined by the standard curve and reported as nanogram IGF-II per 1x10⁶ cells.

IGF-II mRNA measurement. RNAs were made from tumor samples and cDNAs
25 were synthesized. Expression of IGF-II was analyzed on 20 ng of cDNA sample in a Fluorogenic 5'-nuclease PCR assay with specific probes and primers using the ABI Prism 7700 Sequence Detection System (Applied Biosystems; Foster City, CA). CT numbers were normalized by determining Ubiquitin (reference gene) mRNA expression in all samples.

30

IGF2/forward: AGGAGCTCGAGGCGTTCAG (SEQ ID NO: 102)

IGF2/reverse: GTCTTGGGTGGGTAGAGCAATC (SEQ ID NO: 103)

probe: AGGCCAAACGTCACCGTCCCC (SEQ ID NO: 104)

Xenograft models in mice. Four to five million human tumor cells (H322, H838, A2780, ES2, MCF7, SW-527, SK-N-AS, SK-N-MC) in Matrigel were inoculated subcutaneously into each nude mouse. When the tumor size reached at least $\sim 50 \text{ mm}^3$, 19D12/15H12 LCF/HCA treatment was initiated and continued with dosing two times per week. 19D12/15H12 LCF/HCA was injected into each nude mouse, intraperitoneally, at 0.004 mg/mouse, 0.02 mg/mouse, 0.1 mg/mouse or 0.5 mg/mouse. Tumor volumes were measured by Labcat.

IRS-1 phosphorylation level in human lung cancer and normal tissue samples. Twelve pairs of samples of normal and cancerous human lung cancerous tissue samples were obtained from patients. Cell lysates were prepared from the tissue samples and subjected to western blot analysis, staining with anti-phospho-IRS1[pY896] as described above. Total IRS-1 was also measured by staining with an anti-IRS antibody.

The western blot data generated in these experiments is set forth in figure 1. In 6 out of the 12 sample pairs evaluated (50%), greater phospho-IRS-1 levels were observed in tumor tissue samples than in the corresponding normal tissue sample.

Similar results were observed when the level of IRS-1 phosphorylation was measured in normal and cancerous colorectal tissue samples. The colorectal tissue samples were evaluated essentially identically to that way the lung tissue samples were evaluated.

Correlation of *in vivo* efficacy of 19D12/15H12 LCF/HCA with IRS-1 phosphorylation. To evaluate *in vivo* efficacy of 19D12/15H12 LCF/HCA antibody, nude mice bearing human tumor xenografts were administered the antibody or an isotype control, and tumor volume was evaluated over time as described above.

To evaluate IRS-1 phosphorylation in tumor cell lines, cell lines were grown in the presence of absence of 100 ng/ml IGF-I. Cell lysates of A2780, ES2, H322, H838 and SK-N-AS cells were then prepared and evaluated by western blot analysis as describe above.

The results of the *in vivo* efficacy experiments are set forth in figure 2. The 19D12/15H12 LCF/HCA antibody was found to be effective at inhibiting the growth of several types of tumors *in vivo* (e.g., non-small cell lung cancer, ovarian cancer, breast cancer, neuroblastoma).

The results of the experiments measuring basal and IGF-I stimulated IRS-1 phosphorylation in tumor cells are set forth in figure 3. The A2780, H322 and SK-N-AS

cell lines evaluated exhibited the greatest basal and IGF-I stimulated IRS-1 phosphorylation.

The cell lines that were most sensitive, *in vivo*, to growth inhibition by 19D12/15H12 LCF/HCA (figure 2) were those that showed the greatest basal and IGF-I stimulated IRS-1 phosphorylation (figure 3).

IGF-II mRNA expression level in ovarian and colorectal tumor samples.

Normal and cancerous ovarian and colorectal tissue samples were obtained from multiple cancer patients. The level of *IGF-II* mRNA expression was evaluated, by Taqman analysis, as described above. The level of *IGF-II* mRNA expression of each ovarian tissue sample is set forth in figure 4 and the level of *IGF-II* mRNA expression in each colorectal tissue sample is set forth in figure 5. In these experiments, 20% of ovarian tumor samples were found to overexpress *IGF-II* mRNA as compared to normal ovarian tissue samples. Fifty three percent of colorectal samples were found to overexpress *IGF-II* mRNA as compared with adjacent, normal colorectal samples.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Patents, patent applications, Genbank Accession Numbers and publications are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties.

We Claim:

1. A method for treating a tumor in a patient with cancer comprising

(a) selecting a patient or patient population having a tumor known to express one or more
5 of the following:

(i) IRS-1 phosphorylation on tyrosine 896;

(ii) IRS-1 phosphorylation on tyrosine 612;

(iii) IRS-1 phosphorylation on any tyrosine;

10 (iv) IGF-II;

(v) IGF1R phosphorylation on any tyrosine; or

(vi) IGF1R; and

(b) administering to said patient a therapeutically effective amount of an IGF1R inhibitory
15 agent.

2. The method of claim 1 wherein the cancer is selected from the group consisting of
bladder cancer, Wilm's cancer, bone cancer, prostate cancer, lung cancer, non-small cell
lung cancer (NSCLC), colon cancer, rectal cancer, colorectal cancer, endometrial cancer,
20 multiple myeloma, estrogen receptor-positive breast cancer, estrogen receptor-negative
breast cancer, cervical cancer, synovial sarcoma, ovarian cancer, pancreatic cancer,
neuroblastoma, rhabdomyosarcoma, osteosarcoma and vasoactive intestinal peptide
secreting tumors.

25 3. The method of claim 1 wherein the agent is:

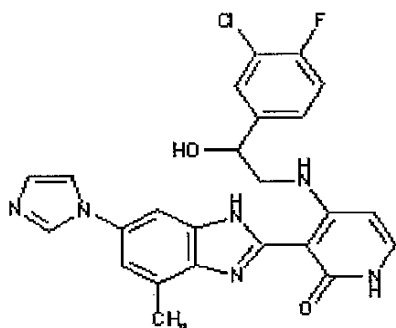
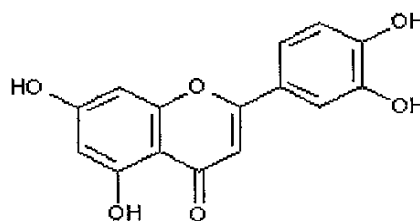
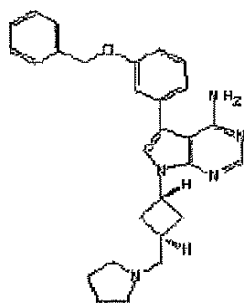
(i) an isolated antibody or antigen-binding fragment thereof that binds specifically to
human IGF1R comprising one or more CDRs from a light chain variable region comprising
amino acids 20-128 of SEQ ID NO: 8 and/or one or more CDRs from a heavy chain
variable region comprising amino acids 20-137 of SEQ ID NO: 10;

30 (ii) an isolated antibody or antigen-binding fragment thereof that binds specifically to
human IGF1R comprising one or more CDRs from a heavy chain immunoglobulin
comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-
98;

(iii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; or

5 (iv) an isolated single-chain antibody (scfv) that binds specifically to human IGF1R comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-51; or

(v)



10

or ATL-1101.

4. The method of claim 3 wherein the isolated antibody or antigen-binding fragment thereof comprises:

- 15 (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98;
- (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72;
- (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791,
- 20 PTA-2789 or PTA-2793;

(iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; or

- 5 (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

10

5. The method of claim 1 wherein phosphorylation of tyrosine on IRS-1 or IGF1R is determined by western blot analysis, ELISA or flow cytometry analysis.

- 15 6. The method of claim 1 wherein IGF-II expression is determined by western blot analysis, ELISA, quantitative PCR or by northern blot analysis.

7. The method of claim 1 wherein IGF1R expression is determined by western blot analysis or ELISA.

- 20 8. A method for treating a tumor in a patient with cancer comprising:
(a) selecting a patient having a tumor expressing one or more of the following:

- 25 (i) IRS-1 phosphorylation on tyrosine 896;
(ii) IRS-1 phosphorylation on tyrosine 612;
(iii) IRS-1 phosphorylation on any tyrosine;
(iv) IGF-II;
(v) IGF1R phosphorylation on any tyrosine; or
(vi) IGF1R; and

- 30 (b) administering to said patient a therapeutically effective amount of an IGF1R inhibitory agent.

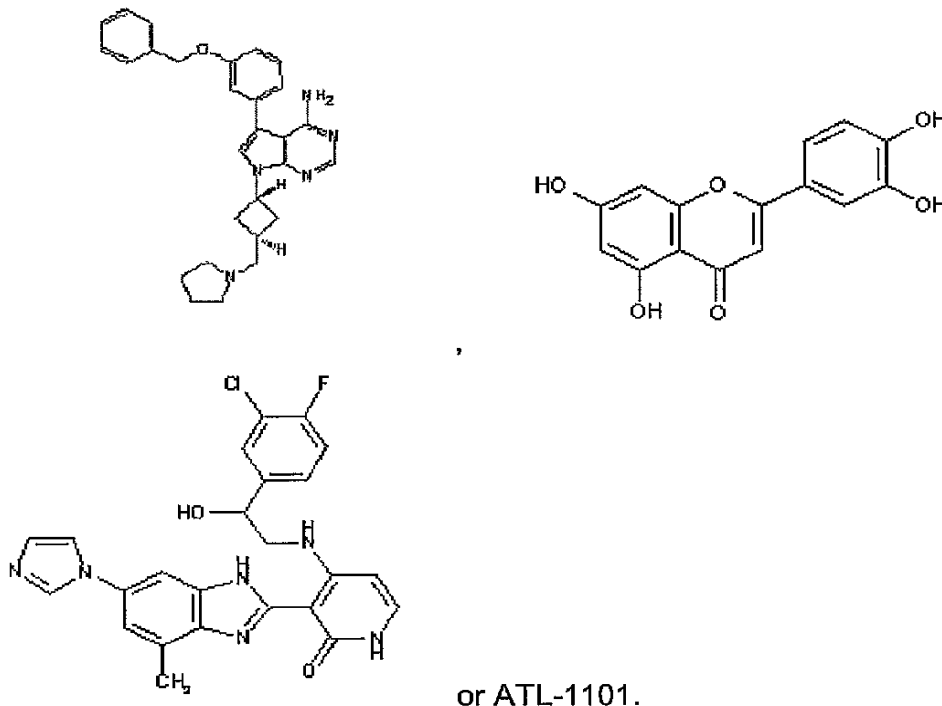
9. The method of claim 8 wherein the cancer is selected from the group consisting of bladder cancer, Wilm's cancer, bone cancer, prostate cancer, lung cancer, non-small cell

lung cancer (NSCLC), colon cancer, rectal cancer, colorectal cancer, endometrial cancer, multiple myeloma, estrogen receptor-positive breast cancer, estrogen receptor-negative breast cancer, cervical cancer, synovial sarcoma, ovarian cancer, pancreatic cancer, neuroblastoma, rhabdomyosarcoma, osteosarcoma and vasoactive intestinal peptide
5 secreting tumors.

10. The method of claim 8 wherein the agent is:

- 10 (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10;
- 15 (ii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98;
- (iii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; or
- 20 (iv) an isolated single-chain antibody (scfv) that binds specifically to human IGF1R comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-51; or
- (v)

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11. The method of claim 10 wherein the isolated antibody or antigen-binding fragment thereof comprises:

- (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98;
- (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72;
- (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793;
- (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; or
- (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

12. The method of claim 8 wherein phosphorylation of tyrosine on IRS-1 or IGF1R is determined by western blot analysis, ELISA or flow cytometry analysis.

5 13. The method of claim 8 wherein IGF-II expression is determined by western blot analysis, ELISA, quantitative PCR or by northern blot analysis.

14. The method of claim 8 wherein IGF1R expression is determined by western blot analysis or ELISA.

10

15. A method for selecting a therapy for a patient or a patient population with a tumor, comprising:

(a) determining whether the patient's tumor is known to express one or more of the following:

15

(i) IRS-1 phosphorylation on tyrosine 896;

(ii) IRS-1 phosphorylation on tyrosine 612;

(iii) IRS-1 phosphorylation on any tyrosine;

(iv) IGF-II;

20

(v) IGF1R phosphorylation on any tyrosine; or

(vi) IGF1R; and

(b) determining whether the patient's tumor expresses one or more of the following:

25

(i) IRS-1 phosphorylation on tyrosine 896;

(ii) IRS-1 phosphorylation on tyrosine 612;

(iii) IRS-1 phosphorylation on any tyrosine;

(iv) IGF-II;

(v) IGF1R phosphorylation on any tyrosine; or

(vi) IGF1R; and

30

(c) selecting an IGF1R inhibitory agent as the therapy if the patient's tumor is known to express one or more of (i)-(vi) and/or if the patient's tumor expresses one or more of (i)-(vi).

16. The method of claim 15 wherein the agent is:

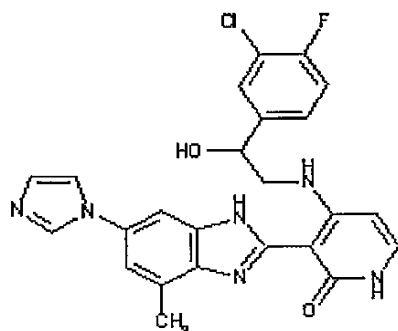
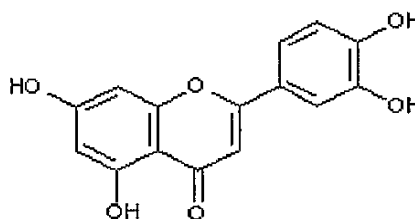
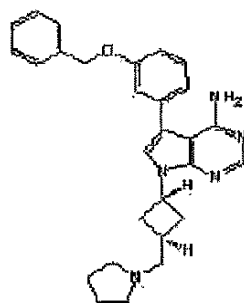
(i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10;

(ii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98;

(iii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; or

(iv) an isolated single-chain antibody (scfv) that binds specifically to human IGF1R comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-51; or

(v)



or ATL-1101.

17. The method of claim 16 wherein the isolated antibody or antigen-binding fragment thereof comprises:

(i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98;

5 (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72;

(iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793;

10 (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; or

15 (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

20 18. The method of claim 12 wherein phosphorylation of tyrosine on IRS-1 or IGF1R is determined by western blot analysis, ELISA or flow cytometry analysis.

19. The method of claim 12 wherein IGF-II expression is determined by western blot analysis, ELISA, quantitative PCR or by northern blot analysis.

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20. The method of claim 12 wherein IGF1R expression is determined by western blot analysis or ELISA.

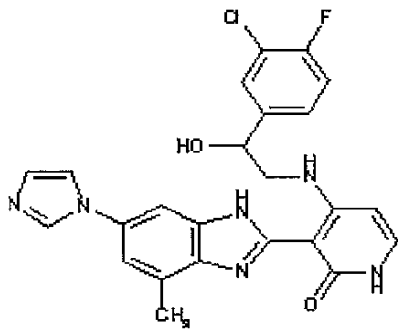
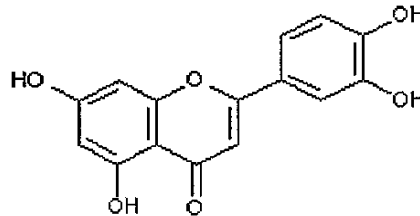
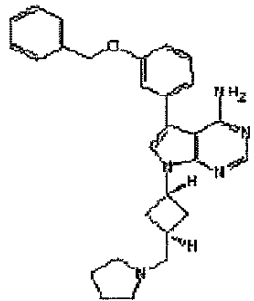
21. A method for advertising an IGF1R inhibitory agent or a pharmaceutically acceptable composition thereof comprising promoting, to a target audience, the use of the agent or pharmaceutical composition thereof for treating a patient or patient population whose tumors express or are known to express one or more of the following:

(i) IRS-1 phosphorylation on tyrosine 896;

- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- 5 (vi) IGF1R.

22. The method of claim 21 wherein the agent is:

- 10 (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10;
- (ii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-15 98;
- (iii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; or
- 20 (iv) an isolated single-chain antibody (scfv) that binds specifically to human IGF1R comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-51; or
- (v)



or ATL-1101.

23. The method of claim 22 wherein the isolated antibody or antigen-binding fragment thereof comprises:

- (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98;
- (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72;
- (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793;
- (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; or
- (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

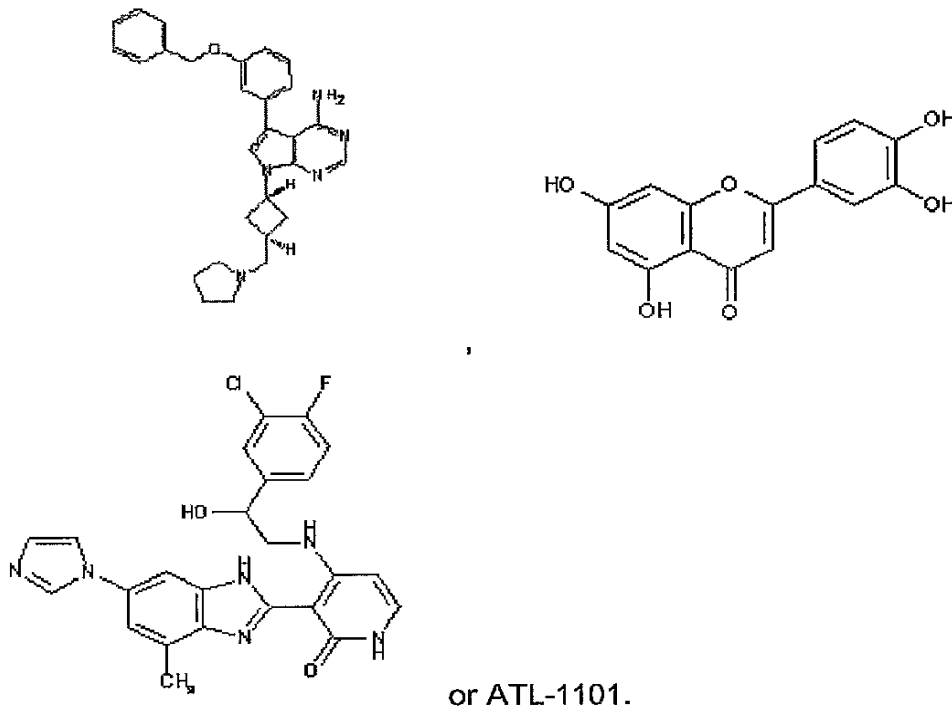
24. An article of manufacture comprising, packaged together, a pharmaceutical composition comprising an IGF1R inhibitory agent and a pharmaceutically acceptable carrier and a label stating that the agent or pharmaceutical composition is indicated for treating patients having a tumor expressing or known to express one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R.

25. The article of claim 24 wherein the agent is:

- (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10;
- (ii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98;
- (iii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; or
- (iv) an isolated single-chain antibody (scfv) that binds specifically to human IGF1R comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-51; or
- (v)

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26. The method of claim 25 wherein the isolated antibody or antigen-binding fragment thereof comprises:

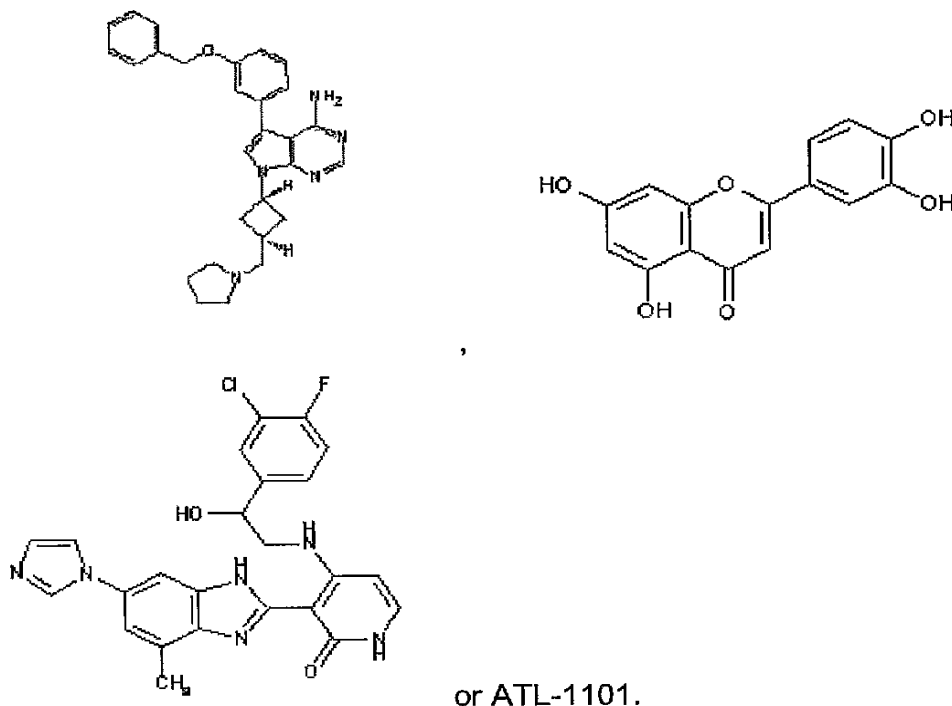
- (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98;
- (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72;
- (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793;
- (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; or
- (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

27. A method for manufacturing an IGF1R inhibitory agent or a pharmaceutical composition thereof comprising combining in a package the agent or pharmaceutical composition and a label stating that the agent or pharmaceutical composition is indicated
5 for treating patients having a tumor expressing or known to express one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- 10 (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R.

15 28. The method of claim 27 wherein the agent is:

- (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10;
- 20 (ii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98;
- (iii) an isolated antibody or antigen-binding fragment thereof that binds specifically to
25 human IGF1R comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; or
- (iv) an isolated single-chain antibody (scfv) that binds specifically to human IGF1R comprising an amino acid sequence selected from the group consisting of SEQ ID NOs:
30 46-51; or
- (v)



29. The method of claim 28 wherein the isolated antibody or antigen-binding fragment thereof comprises:

- (i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98;
- (ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72;
- (iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792; PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793;
- (iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; or
- (v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number PTA-5214 or PTA-5216.

30. A method for identifying a patient whose tumor is likely to be responsive to an IGF1R inhibitory agent comprising:

(a) determining whether the patient has a tumor known to express one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R; and/or

(b) determining whether the patient has a tumor expressing one or more of the following:

- (i) IRS-1 phosphorylation on tyrosine 896;
- (ii) IRS-1 phosphorylation on tyrosine 612;
- (iii) IRS-1 phosphorylation on any tyrosine;
- (iv) IGF-II;
- (v) IGF1R phosphorylation on any tyrosine; or
- (vi) IGF1R.

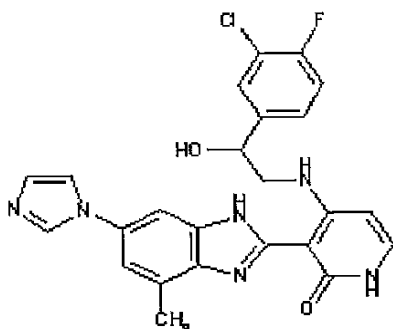
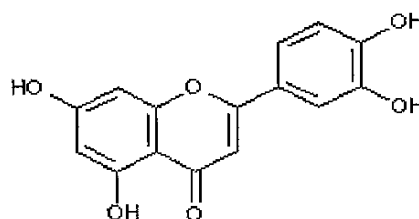
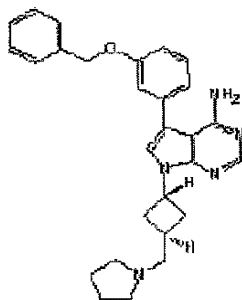
31. The method of claim 30 wherein the agent is:

- (i) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a one or more CDRs from a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10;
- (ii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a heavy chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 19-28, 35-38, 43, 45 or 73-98;
- (iii) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising one or more CDRs from a light chain immunoglobulin comprising the amino acid sequence of SEQ ID NO: 10, 12-18, 29-34, 39, 40, 41, 42, 44 or 58-72; or

(iv) an isolated single-chain antibody (scfv) that binds specifically to human IGF1R comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 46-51; or

(v)

5



or ATL-1101.

32. The method of claim 31 wherein the isolated antibody or antigen-binding fragment thereof comprises:

10

(i) an isolated immunoglobulin heavy chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 19-28, 35-38, 43, 45 and 73-98;

(ii) an isolated immunoglobulin light chain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-18, 29-34, 39, 40, 41, 42, 44 and 58-72;

15

(iii) an isolated antibody produced by a hybridoma deposited at the American Type Culture Collection under deposit number PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789 or PTA-2793;

(iv) an isolated antibody or antigen-binding fragment thereof that binds specifically to human IGF1R comprising a light chain variable region comprising amino acids 20-128 of SEQ ID NO: 8 and/or a heavy chain variable region comprising amino acids 20-137 of SEQ ID NO: 10; or

20

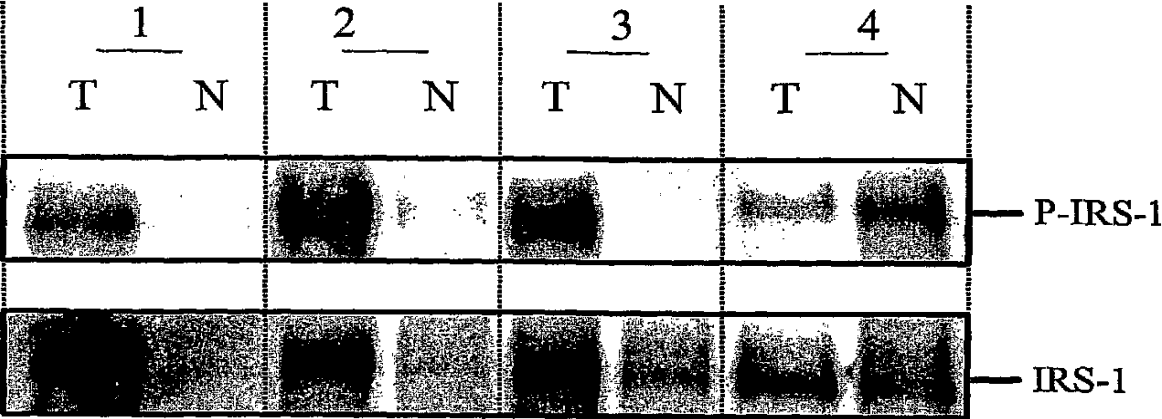
(v) an isolated antibody comprising an immunoglobulin light chain encoded by the plasmid contained in the cell line deposited at the American Type Culture Collection under deposit number PTA-5220 and an immunoglobulin heavy chain encoded by the plasmid contained in a cell line deposited at the American Type Culture Collection under deposit number
5 PTA-5214 or PTA-5216.

33. The method of claim 30 wherein phosphorylation of tyrosine on IRS-1 or IGF1R is determined by western blot analysis, ELISA or flow cytometry analysis.






10 34. The method of claim 30 wherein IGF-II expression is determined by western blot analysis, ELISA, quantitative PCR or by northern blot analysis.

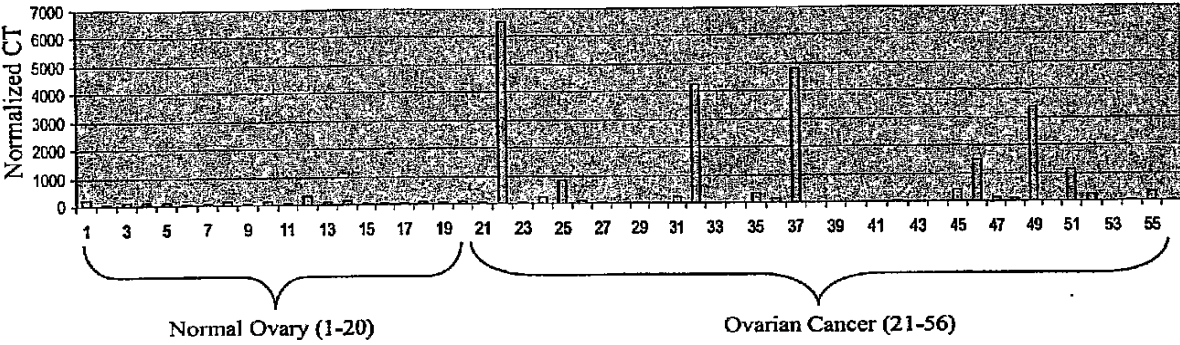
35. The method of claim 30 wherein IGF1R expression is determined by western blot analysis or ELISA.

15



<u>Tumor Type</u>	<u>Maximal Tumor</u>	
<u>Inhibition</u>	<u>Cell Line</u>	<u>Growth</u>
NSCLC	H322	64-102%
NSCLC	H838	24%
Ovarian	A2780	56-63%
Ovarian	ES2	30%
Breast (ER+)	MCF7	68%
Breast (ER-)	SW-527	56%
Neuroblastoma	SK-N-AS	82-87%
Neuroblastoma	SK-N-MC	59%

	A2780 ovarian		ES2 ovarian		H322 NSCLC		H838 NSCLC		SK-N-AS Neurobl.	
IGF-I 100 ng/ml	-	+	-	+	-	+	-	+	-	+
phospho IRS-1 →										
Efficacy in vivo	56-63%		32%		74-102%		24%		82-87%	



5/5

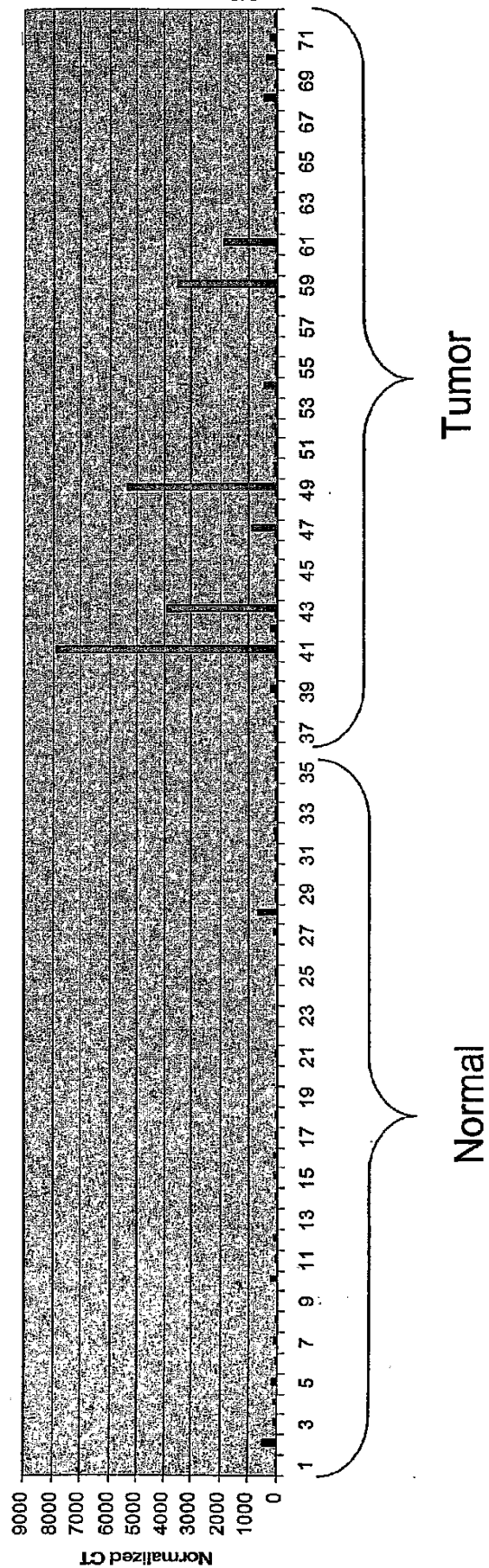


Fig. 5

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 Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
 85 90 95
 ctc gag gct gaa gat gct gca gcg tat tac tgt cat cag agt agt cgt 336
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2

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Thr Pro Gly Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile
 35 40 45

Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
 50 55 60

Leu Leu Ile Lys Tyr Ala Ser Gln Ser Leu Ser Gly Val Pro Ser Arg
 65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
 85 90 95

Leu Glu Ala Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser Arg
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 Ser Arg Gly Glu Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ser Val
 20 25 30

act cca ggc gag aga gtc acc atc acc tgc cgg gcc agt cag agc att 144
 Thr Pro Gly Glu Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile
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 65 70 75 80

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 85 90 95

ctc gag gct gaa gat ttc gca gtg tat tac tgt cat cag agt agt cgt 336
 Leu Glu Ala Glu Asp Phe Ala Val Tyr Tyr Cys His Gln Ser Ser Arg
 100 105 110

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 35 40 45

Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
 50 55 60

Leu Leu Ile Lys Tyr Ala Ser Gln Ser Leu Ser Gly Val Pro Ser Arg
65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
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65 70 75 80
ttc agt ggc agt gga tct ggg aca gat ttc acc ctc acc atc agt aga 288
Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg
85 90 95
ctg gag cct gaa gat gct gca gcg tat tac tgt cat cag agt agt cgt 336
Leu Glu Pro Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser Arg
100 105 110

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Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg
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 35 40 45

7

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Leu Leu Ile Lys Tyr Ala Ser Gln Ser Leu Ser Gly Ile Pro Asp Arg
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 35 40 45

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 85 90 95

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 100 105 110

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Ser Ser Phe Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
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Glu Trp Ile Ser Val Ile Asp Thr Arg Gly Ala Thr Tyr Tyr Ala Asp
 65 70 75 80

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
 85 90 95

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
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 100 105 110

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Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
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Phe Tyr Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
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Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr Thr Leu Tyr Leu
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Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
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 <223> immunoglobulin heavy chain variable region
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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ile Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Leu Gly Tyr Gly Asp Phe Tyr Tyr Tyr Tyr Tyr Gly Met
 100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 17
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> immunoglobulin heavy chain variable region
 <400> 17

Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val
 1 5 10 15

Ser Gly Gly Ser Ile Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro
 20 25 30

14

Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser
35 40 45

Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp
50 55 60

Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala
65 70 75 80

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Thr Tyr Ser Ser Ser Phe Tyr
85 90 95

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210>	18
<211>	122
<212>	PRT
<213>	Artificial Sequence

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<220>
<223> immunoglobulin heavy chain variable region
<400> 18
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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Thr Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

15

Ala Lys Asp Pro Gly Thr Thr Val Ile Met Ser Trp Phe Asp Pro Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 19
 <211> 136
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> immunoglobulin light chain variable region

<400> 19

Ala Ser Val Gly Asp Arg Val Thr Phe Thr Cys Arg Ala Ser Gln Asp
 1 5 10 15

Ile Arg Arg Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
 20 25 30

Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
 35 40 45

Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
 50 55 60

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn
 65 70 75 80

Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Glu Val Glu Ile Ile Arg
 85 90 95

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
 100 105 110

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
 115 120 125

Pro Arg Glu Ala Lys Val Gln Trp
 130 135

<210> 20
 <211> 107
 <212> PRT
 <213> Artificial Sequence

16

<220>

<223> immunoglobulin light chain variable region

<400> 20

Asp	Ile	Gln	Met	Thr	Gln	Phe	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1				5				10						15	

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Arg	Asn	Asp
		20						25					30		

Leu	Gly	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Arg	Leu	Ile
		35					40					45			

Tyr	Ala	Ala	Ser	Arg	Leu	His	Arg	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				

Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80

Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	His	Asn	Ser	Tyr	Pro	Cys
				85					90					95	

Ser	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
				100					105	

<210> 21

<211> 100

<212> PRT

<213> Artificial Sequence

<220>

<223> immunoglobulin light chain variable region

<400> 21

Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	Phe	Thr	Cys	Arg
1				5					10					15	

Ala	Ser	Gln	Asp	Ile	Arg	Arg	Asp	Leu	Gly	Trp	Tyr	Gln	Gln	Lys	Pro
			20					25					30		

Gly	Lys	Ala	Pro	Lys	Arg	Leu	Ile	Tyr	Ala	Ala	Ser	Arg	Leu	Gln	Ser
		35					40					45			

17

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
 50 55 60

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
 65 70 75 80

Leu Gln His Asn Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Glu Val
 85 90 95

Glu Ile Ile Arg
 100

<210> 22
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> immunoglobulin light chain variable region
 <400> 22

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Ser Asp
 20 25 30

Leu Gly Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45

Tyr Ala Ala Ser Lys Leu His Arg Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Arg Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Leu
 85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 23
 <211> 92
 <212> PRT

<213> Artificial Sequence

<220>

<223> immunoglobulin light chain variable region

<400> 23

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Thr
1 5 10 15

Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
20 25 30

Ile His Val Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser
35 40 45

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
50 55 60

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asn Ala Pro
65 70 75 80

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
85 90

<210> 24

<211> 91

<212> PRT

<213> Artificial Sequence

<220>

<223> immunoglobulin light chain variable region

<400> 24

Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Gly Arg Tyr
1 5 10 15

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
20 25 30

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly
35 40 45

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
50 55 60

Glu Asp Phe Ala Val Phe Tyr Cys Gln Gln Tyr Gly Ser Ser Pro Arg
 65 70 75 80

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 85 90

<210> 25
 <211> 236
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin

<400> 25

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
 20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
 35 40 45

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
 65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
 85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
 100 105 110

His Asn Ser Tyr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
 115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 145 150 155 160

20

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235

<210> 26

<211> 236

<212> PRT

<213> Artificial Sequence

<220>

<223> light chain immunoglobulin

<400> 26

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
 20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Phe Thr Cys Arg Ala Ser
 35 40 45

Gln Asp Ile Arg Arg Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val
 65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
 85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
 100 105 110

21

His Asn Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Glu Val Glu Ile
 115 120 125

Ile Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235

<210> 27
 <211> 236
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin

<400> 27

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
 20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
 35 40 45

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
100 105 110

His Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 28

<211> 236

<212> PRT

<213> Artificial Sequence

<220>

<223> light chain immunoglobulin

<400> 28

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

23

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Phe Pro Ser Ser
 20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
 35 40 45

Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu His Arg Gly Val
 65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
 85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
 100 105 110

His Asn Ser Tyr Pro Cys Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile
 115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
 130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
 145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
 165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
 180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
 195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
 210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235

<210> 29
 <211> 473
 <212> PRT

<213> Artificial Sequence

<220>

<223> heavy chain immunoglobulin

<400> 29

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Val Leu Arg Phe Leu Glu Trp Leu Leu Tyr Tyr
115 120 125

Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr
130 135 140

Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
145 150 155 160

Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
165 170 175

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
180 185 190

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
195 200 205

25

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly
 210 215 220
 Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
 225 230 235 240
 Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys
 245 250 255
 Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 260 265 270
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 275 280 285
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
 290 295 300
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
 305 310 315 320
 Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His
 325 330 335
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys 340
 345 350
 Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
 355 360 365
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 370 375 380
 Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 385 390 395 400
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
 405 410 415
 Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
 420 425 430

26

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
 435 440 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
 450 455 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
 465 470

<210> 30
 <211> 470
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin

<400> 30

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
 1 5 10 15

Val Gln Cys Gln Ala Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
 20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 35 40 45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Arg Asp Tyr Ala
 65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
 85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
 100 105 110

Tyr Tyr Cys Val Arg Asp Gly Val Glu Thr Thr Phe Tyr Tyr Tyr Tyr
 115 120 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 130 135 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 145 150 155 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 165 170 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 180 185 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 195 200 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
 210 215 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 225 230 235 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
 245 250 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 260 265 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 275 280 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 305 310 315 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
 325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
 355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 405 410 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 450 455 460

Ser Leu Ser Pro Gly Lys
 465 470

<210> 31
 <211> 470
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin

<400> 31

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
 1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
 20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 35 40 45

Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala
 65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
 85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
 100 105 110

Tyr Tyr Cys Ala Lys Gly Tyr Ser Ser Gly Trp Tyr Tyr Tyr Tyr Tyr
 115 120 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 130 135 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 145 150 155 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 165 170 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser 180
 185 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 195 200 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
 210 215 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 225 230 235 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
 245 250 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 260 265 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 275 280 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 305 310 315 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
 325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
 355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 405 410 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 450 455 460

Ser Leu Ser Pro Gly Lys
 465 470

<210> 32
 <211> 470
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin

<400> 32
 Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
 1 5 10 15

Val Gln Cys Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
 20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe
 35 40 45

Ser Ser Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Thr Thr Phe Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Thr
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Lys Asp Leu Gly Trp Ser Asp Ser Tyr Tyr Tyr Tyr
115 120 125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
130 135 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
145 150 155 160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
165 170 175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
180 185 190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
195 200 205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
210 215 220

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
225 230 235 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
245 250 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
260 265 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
275 280 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 305 310 315 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
 325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
 355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 405 410 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 435 440 445

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 450 455 460

Ser Leu Ser Pro Gly Lys
 465 470

<210> 33
 <211> 470
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> immunoglobulin heavy chain of 2.12.1 fx

<400> 33

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Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1           5           10           15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
          20           25           30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
          35           40           45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
50           55           60

Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Arg Asp Tyr Ala
65           70           75           80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
          85           90           95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
          100          105          110

Tyr Tyr Cys Ala Arg Asp Gly Val Glu Thr Thr Phe Tyr Tyr Tyr Tyr
          115          120          125

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          130          135          140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
          145          150          155          160

Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
          165          170          175

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
          180          185          190

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
          195          200          205

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
          210          215          220

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Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 225 230 235 240

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
 245 250 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
 260 265 270

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 275 280 285

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
 290 295 300

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
 305 310 315 320

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
 325 330 335

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
 340 345 350

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
 355 360 365

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
 370 375 380

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
 385 390 395 400

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
 405 410 415

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
 420 425 430

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
 435 440 445

35

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 450 455 460

Ser Leu Ser Pro Gly Lys
 465 470

<210> 34
 <211> 125
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> mature immunoglobulin heavy chain variable region of 2.12.1 fx
 <400> 34

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
 20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Arg Asp Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Asp Gly Val Glu Thr Thr Phe Tyr Tyr Tyr Tyr Tyr Gly Met
 100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 35
 <211> 236
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> immunoglobulin light chain of 2.12.1 fx

<400> 35

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1          5          10          15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
          20          25          30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
          35          40          45

Gln Asp Ile Arg Arg Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys
          50          55          60

Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val
65          70          75          80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
          85          90          95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
          100          105          110

His Asn Asn Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
          115          120          125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
          130          135          140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145          150          155          160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
          165          170          175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
          180          185          190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
          195          200          205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
          210          215          220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225          230          235

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37

<210> 36
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> mature immunoglobulin light chain variable region of 2.12.1 fx
 <400> 36

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Arg Asp
 20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
 35 40 45

Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Asn Tyr Pro Arg
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 37
 <211> 112
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> humanized 7C10 immunoglobulin light chain variable region;
 version 1

<400> 37

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

38

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Tyr Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 38

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized 7C10 immunoglobulin light chain variable region;
 version 2

<400> 38

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Gly Asn Thr Tyr Leu Gln Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Leu Tyr Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

39

Ser His Val Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 39
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> humanized 7C10 immunoglobulin heavy chain variable region;
 version 1

<400> 39

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Gly Gly
 20 25 30

Tyr Leu Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Met Gly Tyr Ile Ser Tyr Asp Gly Thr Asn Asn Tyr Lys Pro Ser Leu
 50 55 60

Lys Asp Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Tyr Gly Arg Val Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> 40
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> humanized 7C10 immunoglobulin heavy chain variable region;
 version 2

<400> 40

40

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Thr Gly Gly
 20 25 30

Tyr Leu Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Ile Gly Tyr Ile Ser Tyr Asp Gly Thr Asn Asn Tyr Lys Pro Ser Leu
 50 55 60

Lys Asp Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
 65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Tyr Gly Arg Val Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser
 115

<210> 41

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> humanized 7C10 immunoglobulin heavy chain variable region;
 version 3

<400> 41

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Tyr Ser Ile Ser Gly Gly
 20 25 30

Tyr Leu Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
 35 40 45

Ile Gly Tyr Ile Ser Tyr Asp Gly Thr Asn Asn Tyr Lys Pro Ser Leu
 50 55 60

Lys Asp Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Gly Arg Val Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 42
<211> 130
<212> PRT
<213> Artificial Sequence

<220>
<223> A12 immunoglobulin heavy chain variable region
<400> 42

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Pro Leu Arg Phe Leu Glu Trp Ser Thr Gln Asp His Tyr
100 105 110

Tyr Tyr Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val
115 120 125

42

Ser Ser
130

<210> 43
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> A12 immunoglobulin light chain variable region

<400> 43

Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Gly Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
50 55 60

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Asn Ser Asp Asn Arg
85 90 95

Leu Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Ser
100 105

<210> 44
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> 1A immunoglobulin heavy chain variable region

<220>
<221> MISC_FEATURE
<222> (1)..(119)
<223> Possible mutations: R30, S30, N31, S31, Y94, H94, D104, E104.

<400> 44

43

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val His Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe Arg Asn Tyr
 20 25 30

Ala Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Gly Ser Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys
 50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
 65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr Tyr Cys Ala
 85 90 95

Arg Ala Pro Asn Trp Gly Ser Asp Ala Phe Asp Ile Trp Gly Gln Gly
 100 105 110

Thr Met Val Thr Val Ser Ser
 115

<210> 45
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> 1A immunoglobulin light chain variable region

<220>
 <221> MISC_FEATURE
 <222> (1)..(107)
 <223> possible mutations: P96, I96, P100, Q100, R103, K103, V104, L104,
 D105, E105 .

<400> 45

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20 25 30

44

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Pro
 85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 46
 <211> 251
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> single chain fv 8A1

<400> 46

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Leu Thr Ile Ser Cys Lys Gly Pro Gly Tyr Asn Phe Phe Asn Tyr
 20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Tyr Pro Thr Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60

Gln Gly Gln Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95

Ala Arg Ser Ile Arg Tyr Cys Pro Gly Gly Arg Cys Tyr Ser Gly Tyr
 100 105 110

45

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
 115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser
 130 135 140

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
 145 150 155 160

Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp
 165 170 175

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
 180 185 190

Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
 195 200 205

Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
 210 215 220

Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
 225 230 235 240

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 245 250

<210> 47
 <211> 245
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> single chain fv 9A2

<400> 47

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Arg Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Thr Ser Gly Tyr Thr Phe Arg Asn Tyr
 20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45

46

Gly Arg Ile Ser Gly His Tyr Gly Asn Thr Asp His Ala Gln Lys Phe
 50 55 60

Gln Gly Arg Phe Thr Met Thr Lys Asp Thr Ser Thr Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Arg Ser Leu Thr Phe Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Ser Gln Trp Asn Val Asp Tyr Trp Gly Arg Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
 115 120 125

Gly Gly Ser Ala Leu Asn Phe Met Leu Thr Gln Pro His Ser Val Ser
 130 135 140

Glu Ser Pro Gly Lys Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly
 145 150 155 160

Ser Ile Ala Ser Asn Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser
 165 170 175

Ser Pro Thr Thr Val Ile Phe Glu Asp Asn Arg Arg Pro Ser Gly Val
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Ile Asp Thr Ser Ser Asn Ser Ala Ser
 195 200 205

Leu Thr Ile Ser Gly Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys
 210 215 220

Gln Ser Phe Asp Ser Thr Asn Leu Val Val Phe Gly Gly Gly Thr Lys
 225 230 235 240

Val Thr Val Leu Gly
 245

<210> 48
 <211> 245
 <212> PRT
 <213> Artificial Sequence

<220>

<223> single chain fv 11A4

<400> 48

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Ser Ser Pro Tyr Ser Ser Arg Trp Tyr Ser Phe Asp Pro Trp Gly
 100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
 115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Tyr Glu Leu Thr Gln
 130 135 140

Pro Pro Ser Val Ser Val Ser Pro Gly Gln Thr Ala Thr Ile Thr Cys
 145 150 155 160

Ser Gly Asp Asp Leu Gly Asn Lys Tyr Val Ser Trp Tyr Gln Gln Lys
 165 170 175

Pro Gly Gln Ser Pro Val Leu Val Ile Tyr Gln Asp Thr Lys Arg Pro
 180 185 190

Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Ile Ala
 195 200 205

48

Thr Leu Thr Ile Ser Gly Thr Gln Ala Val Asp Glu Ala Asp Tyr Tyr
 210 215 220

Cys Gln Val Trp Asp Thr Gly Thr Val Val Phe Gly Gly Gly Thr Lys
 225 230 235 240

Leu Thr Val Leu Gly
 245

<210> 49
 <211> 251
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> single chain fv 7A4

<400> 49

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Leu Thr Ile Ser Cys Lys Gly Ser Gly Tyr Asn Phe Phe Asn Tyr
 20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Asp Leu Glu Trp Met
 35 40 45

Gly Ile Ile Tyr Pro Thr Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60

Gln Gly Gln Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95

Ala Arg Ser Ile Arg Tyr Cys Pro Gly Gly Arg Cys Tyr Ser Gly Tyr
 100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
 115 120 125

Gly Gly Gly Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser
 130 135 140

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
 145 150 155 160

Arg Ile Thr Cys Arg Gly Asp Ser Leu Arg Asn Tyr Tyr Ala Ser Trp
 165 170 175

Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys
 180 185 190

Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
 195 200 205

Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
 210 215 220

Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Met Val
 225 230 235 240

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 245 250

<210> 50
 <211> 249
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> single chain fv 11A1

<400> 50

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Phe
 20 25 30

Ala Met His Trp Val Arg Gln Ile Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45

Ser Gly Leu Arg His Asp Gly Ser Thr Ala Tyr Tyr Ala Gly Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Val Tyr
 65 70 75 80

Lys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Pro	Pro	Ser	Ala	Ser	Gly	Thr	Pro	Gly	Gln	Arg	Val	Thr	Ile	Ser	Cys
145					150					155					160

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Ser Asn Asn Gln
180 185 190

Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp
210 215 220

Gly Gly Thr Lys Val Thr Val Leu Gly
245

<400> 51

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Thr Ile Ser Cys Lys Gly Ser Gly Tyr Asn Phe Phe Asn Tyr
 20 25 30

Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45

Gly Ile Ile Tyr Pro Thr Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60

Gln Gly Gln Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95

Ala Arg Ser Ile Arg Tyr Cys Pro Gly Gly Arg Cys Tyr Ser Gly Tyr
 100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser
 130 135 140

Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val
 145 150 155 160

Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Thr Asn Trp
 165 170 175

Phe Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu Val Val Tyr Ala Lys
 180 185 190

Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser
 195 200 205

Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu
 210 215 220

Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
 225 230 235 240

52

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
245 250

<210> 52
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 52

Ser Tyr Trp Met His
1 5

<210> 53
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 53

Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Arg

<210> 54
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 54

Gly Arg Pro Asp Tyr Tyr Gly Ser Ser Lys Trp Tyr Phe Asp Val
1 5 10 15

<210> 55
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> CDR

<400> 55

53

Arg Ser Ser Gln Ser Ile Val His Ser Asn Val Asn Thr Tyr Leu Glu
 1 5 10 15

<210> 56
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDR

<400> 56

Lys Val Ser Asn Arg Phe Ser
 1 5

<210> 57
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> CDR

<400> 57

Phe Gln Gly Ser His Val Pro Pro Thr
 1 5

<210> 58
 <211> 123
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin variable region

<400> 58

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Gln Lys Phe
 50 55 60

54

Gln Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Phe
85 90 95

Ala Arg Gly Arg Pro Asp Tyr Tyr Gly Ser Ser Lys Trp Tyr Phe Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser 115 120

<210> 59

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> heavy chain immunoglobulin variable region

<400> 59

Gln Val Gln Phe Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Leu Met His Trp Ile Lys Gln Arg Pro Gly Arg Gly Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Asn Asn Val Val Thr Lys Phe Asn Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Pro Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Ala Tyr Cys Arg Pro Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

55

<210> 60
 <211> 123
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin variable region

<400> 60

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe
 50 55 60

Lys Arg Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Phe
 85 90 95

Ala Arg Gly Arg Pro Asp Tyr Tyr Gly Ser Ser Lys Trp Tyr Phe Asp
 100 105 110

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser
 115 120

<210> 61
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin variable region

<400> 61

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Met Lys Pro Gly Ala
 1 5 10 15

56

Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Phe
 20 25 30

Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Leu Pro Gly Ser Gly Gly Thr His Tyr Asn Glu Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly His Ser Tyr Tyr Phe Tyr Asp Gly Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Ser Val Thr Val Ser Ser
 115 120

<210> 62

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> heavy chain immunoglobulin variable region

<400> 62

Gln Val Gln Leu Gln Gln Pro Gly Ser Val Leu Val Arg Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Ser
 20 25 30

Trp Ile His Trp Ala Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile His Pro Asn Ser Gly Asn Thr Asn Tyr Asn Glu Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
 65 70 75 80

57

Val Asp Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Trp Arg Tyr Gly Ser Pro Tyr Tyr Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
 115 120

<210> 63

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> heavy chain immunoglobulin variable region

<400> 63

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Tyr Asn Glu Lys Phe
 50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Pro Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Tyr Asp Tyr Tyr Gly Ser Ser Tyr Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
 115 120

<210> 64

<211> 123

<212> PRT

<213> Artificial Sequence

<220>

58

<223> heavy chain immunoglobulin variable region

<400> 64

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Gln Lys Phe
 50 55 60

Gln Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Phe
 85 90 95

Ala Arg Gly Arg Pro Asp Tyr Tyr Gly Ser Ser Lys Trp Tyr Phe Asp
 100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
 115 120

<210> 65

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> heavy chain immunoglobulin variable region

<400> 65

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe
 50 55 60

Lys Arg Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Phe
85 90 95

Ala Arg Gly Arg Pro Asp Tyr Tyr Gly Ser Ser Lys Trp Tyr Phe Asp
100 105 110

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 66
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain immunoglobulin variable region

<400> 66

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Gln Lys Phe
50 55 60

Gln Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Phe
85 90 95

Ala Arg Gly Arg Pro Asp Tyr Tyr Gly Ser Ser Lys Trp Tyr Phe Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

60

<210> 67
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin variable region
 <400> 67

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Arg Gly Leu Glu Trp Ile
 35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Tyr Asn Glu Lys Phe
 50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Pro Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Tyr Asp Tyr Tyr Gly Ser Ser Tyr Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 68
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin variable region
 <400> 68

Gln Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Arg Pro Gly Ala
 1 5 10 15

61

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Tyr Ile His Trp Val Lys Gln Arg Pro Gly Glu Gly Leu Glu Trp Ile
 35 40 45

Gly Trp Ile Tyr Pro Gly Ser Gly Asn Thr Lys Tyr Asn Glu Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
 85 90 95

Ala Arg Gly Gly Lys Phe Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
 100 105 110

Val Thr Val Ser Ser
 115

<210> 69
 <211> 124
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin variable region

<400> 69

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe
 50 55 60

Lys Arg Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
 65 70 75 80

62

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Phe
 85 90 95

Ala Arg Gly Arg Pro Asp Tyr Tyr Gly Ser Ser Lys Trp Tyr Phe Asp
 100 105 110

Val Trp Gly Ala Gly Thr Thr Val Thr Val Ser Ser
 115 120

<210> 70
 <211> 120
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> heavy chain immunoglobulin variable region

<400> 70

Gln Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30

Tyr Ile Asn Trp Met Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45

Gly Trp Ile Asp Pro Gly Ser Gly Asn Thr Lys Tyr Asn Glu Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys
 85 90 95

Ala Arg Glu Lys Thr Thr Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Ser Val Thr Val Ser Ala
 115 120

<210> 71
 <211> 115

63

<212> PRT

<213> Artificial Sequence

<220>

<223> heavy chain immunoglobulin variable region

<400> 71

Val	Gln	Leu	Gln	Gln	Ser	Gly	Ala	Glu	Leu	Met	Lys	Pro	Gly	Ala	Ser
1			5						10					15	

Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Ser	Asp	Tyr	Trp
			20					25					30		

Ile	Glu	Trp	Val	Lys	Gln	Arg	Pro	Gly	His	Gly	Leu	Glu	Trp	Ile	Gly
		35					40					45			

Glu	Ile	Leu	Pro	Gly	Ser	Gly	Ser	Thr	Asn	Tyr	His	Glu	Arg	Phe	Lys
	50					55					60				

Gly	Lys	Ala	Thr	Phe	Thr	Ala	Asp	Thr	Ser	Ser	Ser	Thr	Ala	Tyr	Met
65					70					75					80

Gln	Leu	Asn	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Leu
				85					90					95	

His	Gly	Asn	Tyr	Asp	Phe	Asp	Gly	Trp	Gly	Gln	Gly	Thr	Thr	Leu	Thr
			100					105					110		

Val	Ser	Ser
		115

<210> 72

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> heavy chain immunoglobulin variable region

<400> 72

Gln	Val	Gln	Leu	Leu	Glu	Ser	Gly	Ala	Glu	Leu	Met	Lys	Pro	Gly	Ala
1			5						10					15	

Ser	Val	Lys	Ile	Ser	Cys	Lys	Ala	Thr	Gly	Tyr	Thr	Phe	Ser	Ser	Phe
			20					25					30		

64

Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Leu Pro Gly Ser Gly Gly Thr His Tyr Asn Glu Lys Phe
 50 55 60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Lys Ser Ser Asn Thr Ala Tyr
 65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly His Ser Tyr Tyr Phe Tyr Asp Gly Asp Tyr Trp Gly Gln
 100 105 110

Gly Thr Ser Val Thr Val Ser Ser
 115 120

<210> 73
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 73

Asp Val Leu Met Thr Gln Ile Pro Val Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ile Ile Val His Asn
 20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

65

Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 74
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 74

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 75
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 75

66

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 76
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 76

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

67

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 77
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 77

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

68

<210> 78
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<220>
 <221> misc_feature
 <222> (28)..(28)
 <223> Xaa can be any naturally occurring amino acid

<220>
 <221> misc_feature
 <222> (101)..(101)
 <223> Xaa can be any naturally occurring amino acid
 <400> 78

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Xaa Ile Val His Ser
 20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Xaa Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 79
 <211> 113
 <212> PRT

69

<213> Artificial Sequence

<220>

<223> light chain immunoglobulin variable region

<400> 79

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 80

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> light chain immunoglobulin variable region

<400> 80

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

70

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 81
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 81

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 82
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 82

Asp Val Leu Met Thr Gln Ile Pro Val Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ile Ile Val His Asn
 20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 83
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 83

72

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Phe Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Ser Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 84
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 84

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

73

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 85
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 85

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

74

<210> 86
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 86

Glu Leu Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Thr Ile Val His Ser
 20 25 30

Asn Gly Asp Thr Tyr Leu Asp Trp Phe Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 87
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 87

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

75

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 88

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> light chain immunoglobulin variable region

<400> 88

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

76

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 89
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 89

Asp Val Leu Met Thr Gln Thr Pro Val Ser Leu Ser Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Thr Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Ala
 85 90 95

Ser His Ala Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 90
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

77

<400> 90

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Ser Gly Asn Thr Tyr Phe Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Ile Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 91

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> light chain immunoglobulin variable region

<400> 91

Asp Ile Glu Leu Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro

78

50		55		60	
Asp Arg Phe Ser Gly	Ser Gly Ser Gly Thr	Asp Phe Thr Leu Lys Ile			
65	70	75		80	
Ser Arg Val Glu Ala Glu Asp Leu Gly	Val Tyr Tyr Cys Phe Gln Gly				
	85	90		95	
Ser His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys					
	100	105		110	

Arg

<210> 92
 <211> 113
 <212> PRT

<213> Artificial Sequence

<220>

<223> light chain immunoglobulin variable region

<400> 92

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> 93
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 93

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Asp Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Val Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 94
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region

<400> 94

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
 1 5 10 15

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Arg Ile
65 70 75 80

81

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 96
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> light chain immunoglobulin variable region
 <400> 96

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
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Asp Gln Ala Ser Ile Ser Cys Arg Ser Asn Gln Thr Ile Leu Leu Ser
 20 25 30

Asp Gly Asp Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 97
 <211> 113
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<400> 97

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
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Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Thr Ile Val His Ser
 20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Thr Asn Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Thr His Ala Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 98

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<213> Artificial Sequence

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<223> light chain immunoglobulin variable region

<400> 98

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
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Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
 20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45

Pro Lys Leu Leu Ile Tyr Ser Ile Ser Ser Arg Phe Ser Gly Val Pro
 50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80

Ser Arg Val Gln Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
 85 90 95

Ser His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
 100 105 110

Arg

<210> 99
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<220>
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<400> 99
 ctccgcttcc ttcc 14

<210> 100
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<210> 101
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<400> 101
 atctctccgc ttcccttc 18

<210> 102

<211> 19
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<400> 102
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19

<210> 103
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 <212> DNA
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<220>
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<400> 103
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22

<210> 104
 <211> 21
 <212> DNA
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<400> 104
 aggccaaacg tcaccgtccc c

21

<210> 105
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Ser Ser Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
 1 5 10 15

Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
 20 25 30

Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Ile Leu Val Ile Tyr
 35 40 45

Gly Glu Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
 50 55 60

85

Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Lys Ser Arg Asp Gly Ser Gly Gln His
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105